PROCEEDINGS
OF THE
ROYAL SOCIETY OF MEDICINE

Vol. 49 No. 3 March 1956

**NOTICE**

The Honorary Editors regret that this issue of the "Proceedings" is greatly reduced in size. This small number is due to the dispute in the Printing Trade.

## CONTENTS



*Continued overleaf*

CONTENTS (*continued*)



*N.B.— The Society does not hold itself in any way reponsible for the statements made or the views put forward in the various papers.*

# Section of Dermatology

President—LOUIS FORMAN, M.D., F.R.C.P.

[*October* 20, 1955]

**Sustained Blood Eosinophilia with ? Eosinophilic Granulomata.**—D. S. WILKINSON, M.D., M.R.C.P.

Mrs. L. G., aged 74.

April 1954 : Generalized pruritus of more than a year's duration. A blotchy erythema was present on the trunk. This faded in a few days and has not recurred. (She had been taking phenobarbitone.) Since then she has been seen on a number of occasions with a variable degree of pruritus which has been less marked in the last six months. An eczematous eruption occurs from time to time. No vesicles have ever been observed. Occasional outbreaks of prurigo have occurred. The main feature has been the variability and inconsistency of the skin changes. There has been no constant relation with the blood changes, though the itching has been less since the eruption of the granulomata and with the lower level of eosinophilia.

May 1955: She developed the first of a series of large, irregular, purplish, infiltrated lesions, for the most part on the flanks and chest wall. These arise dramatically within a space of a few hours and cause pain and discomfort. They subside slowly and the residual thickening and discoloration of the skin persist for two to three weeks.

*Clinical findings.*—Careful and full examination on several occasions has revealed no outstanding abnormality, though at one time her liver and spleen were thought to be palpable. This was not confirmed later. There is no albuminuria.

*Investigations.*—There has been a persistent and marked eosinophilia. Except for one occasion a year ago when the eosinophils dropped to 1% the absolute and percentage values have been over double the acceptable upper limit of 5% consistently on over twenty occasions. There has been some leucopenia (except on the occasion when the eosinophils became normal and the total white cell count rose to 10,000/c.mm.). On admission in April 1954 she was given a test course of three days' cortisone (150–100 mg.); no effect on itching or on eosinophils.

*Iliac crest puncture* (6.5.54).—"No evidence of leukæmia and no increase in eosinophils. The most striking feature is a hyperplasia of erythropoietic tissue (myeloid–erythroid ratio =1 : 1·8), normoblastic in type, and the presence of nucleated remnants in many of the normoblasts (Howell-Jolly bodies). Reticulocytes 3%."

*Sternal marrow puncture* (23.8.55).—"This yielded a cellular marrow, with marked normoblastic hyperplasia. About one-third of the nucleated red cells contain nuclear fragments. The myeloid-erythroid ratio is 1 : 1·8. There is a relative increase in eosinophils, but no suggestion of leukæmia. Reticulocytes 3%."

27.10.54–1.12.54: Alkaline phosphatase 5 K.A. units; plasma proteins, serum cholesterol, and liver function tests were all normal.

No ova or cysts seen on repeated stool examination. Bence-Jones proteoses absent (twice).

Platelets 291,000/c.mm. E.S.R. 4 mm. in one hour (Westergren). Blood fragility normal. Coombs test negative. Reticulocytes 2/100 red blood cells. "There is an occasional immature cell of both the neutrophil and eosinophil series present. The red cells show anisocytosis, and the persistence of an occasional nucleated red cell with Howell-Jolly bodies." Plasma bilirubin 1·7 mg.–2 mg./100 ml. (on 3 occasions).

X-rays (9.6.55): Chest normal. Right shoulder: "frozen" shoulder ("post-traumatic"). Skull: "There are many circular translucencies which suggest the presence of myelomatosis. The condition might be caused by changes due to eosinophilic granuloma of the bone but there is nothing characteristic or distinctive in the appearance of eosinophilic granuloma, and the former diagnosis is the more likely one, especially as the latter is an affection of the young."

*Biopsy report* 19.10.55 (Dr. H. Haber).—"The epidermis does not show any appreciable changes. The mid- and low cutis shows a very marked infiltration situated within tissue spaces. It consists of masses of histiocytes containing a vesicular nucleus and abundant cytoplasm. In some places the cytoplasm shows a foamy appearance. These cells fuse to produce small histiocytic giant cells. Some look like Langerhans cells and some like foreign body giant cells.

"The next cell which is conspicuous is the eosinophil cell. There are also a few round cells demonstrable. There are several foci of collagenous degeneration leading to fragmentation and basophilic staining of disintegrating collagen bundles and one can see quite distinctly

the histiocytes arranged in a palisade around some of the foci. The histology suggests a widespread granuloma annulare exemplified by localized changes of the collagen to which the histiocytes respond in the characteristic manner. The presence of eosinophils might indicate an allergic process."

15.12.55.—She has again been investigated in hospital without any significant new findings. ACTH (long-acting) 40 units per day depressed the eosinophils and prevented eruption of granulomata; oral cortisone, 75 mg. daily, did not do so.

*Comment.*—Both dermatitis herpetiformis and senile prurigo were originally considered as possible diagnoses. But the sustained eosinophilia persisted despite periods of complete freedom from itching and she failed to respond to adequate doses of sulphones, sulphapyridine or antihistamines. There has been no evidence of malignant disease or leukæmia. Although this possibility remains, one would have expected some evidence of it by now.

Dr. Haber has studied the sections most carefully and considers that the reaction represents a granuloma annulare. The lesions clinically resemble those in Lewis and Cormia's case but the histological features are quite different. Woerdeman and Prakken, in their extensive study of this condition, place Lewis' case in the group due to non-specific infections. It seems likely that the patient reported here may have some yet undiscovered source of a toxic or allergic reaction that gives rise to her eosinophilia (with concomitant neutropenia) and to these granulomata.

## REFERENCES

LEWIS, G. M., and CORMIA, F. E. (1947) *Arch. Derm. Syph., Chicago*, **55**, 176.
WOERDEMAN, M. J., and PRAKKEN, J. R. (1952) *Dermatologica, Basel*, **105**, 133.

**Dr. C. H. Whittle:** Dr. Wilkinson drew attention to the variation of the neutrophil count in the course of the disease, and it seemed that this afforded some index of the activity of the disease. I have observed a similar depression of the neutrophil count in other disorders, notably in a case of disseminate L.E. shown here (*Brit. J. Derm.*, 1952, **64**, 295). The count remained low during the active phase of the disease and rose to normal as the patient recovered. Once or twice the patient has shown a transitory tendency to relapse which was accompanied by a slight depression of the neutrophil count.

**Dr. Wilkinson:** I think that is true. In the early stages, when the itching was most severe the disparity was most marked. As the symptoms became less the blood picture approximated towards normal, but the granulomata appeared. At that time the neutrophil count increased a little. I regarded the depression of leucocytes as suggesting some toxic process.

**Dr. J. T. Ingram:** We have a similar case, a female patient in her fifties in whom we feel these are the expressions of malignant disease in the chest. I cannot help thinking in relation to this case that the lesions are dependent upon malignant disease.

POSTSCRIPT (14. 2. 56).—Malignant disease of chest was later found.—J.T.I.

**Acquired Ichthyosis Following Parapsoriasis en Plaque.**—BRIAN RUSSELL, M.D., F.R.C.P.

A. B., male, aged 56. Clerk.

*History.*—In 1951 he developed non-itchy, pinkish-brown, slightly scaly, oval patches on the skin of the legs, and later on the thighs, arms and trunk. There was some diffuse atrophy of the skin of the trunk and calves. No lymphadenopathy.

*Investigations.*—Wassermann reaction negative. X-ray of chest: no abnormality detected. Mantoux reaction negative 1/100. Blood count within normal limits. Biopsy from left arm showed slight patchy hyperkeratosis and parakeratosis, with some atrophy of epidermis. Slight œdema and non-specific infiltration in the upper dermis.

*Treatment and prognosis.*—Between November 1952 and April 1954 he was treated with calciferol, vitamin A, general ultraviolet irradiation and thorium X, without benefit. During a course of mepacrine the lesions became more conspicuously yellow than the adjoining skin. There has been no active treatment since April 1954.

Since August 1954 the lesions have become inconspicuous and the general appearance more ichthyosiform.

According to Hoyle *et al.* (1954) tuberculin insensitivity is an attribute of reticuloendothelial disorders in general. Is the negative Mantoux reaction at 1/100 in this patient a clue indicating that he may have that type of parapsoriasis en plaque which terminates in a reticulosis? Has he in fact a reticulosis now?

An increasing number of persons to-day are negative Mantoux reactors and for this reason the negative finding in this patient is of no significance in itself. It is important to determine whether the Mantoux reaction remains negative after B.C.G. inoculation. A normal reaction has so far developed after the B.C.G. inoculation and the Mantoux reaction will be retested in three months' time.

Nanta and Chatellier (1925) described ichthyosiform hyperkeratoses in Hodgkin's disease. Ronchese (1943) stated that atrophy, keratoses and pigmentation are some of the nonspecific cutaneous manifestations of Hodgkin's disease. Sneddon (1955) has recently stressed that

acquired ichthyosiform atrophy may be a manifestation of Hodgkin's disease or lymphoblastoma.

REFERENCES

HOYLE, C., DAWSON, J., and MATHER, G. H. (1954) *Lancet*, ii, 164.
NANTA, A., and CHATELLIER, L. (1925) *Ann. Derm. Syph., Paris*, **6**, 682.
RONCHESE, F. (1943) *Arch. Derm. Syph., Chicago*, **47**, 778.
SNEDDON, I. B. (1955) *Brit. med. J.*, i, 763.

**Dr. R. D. Sweet:** Is it known whether those patients with Hodgkin's disease have originally had a positive reaction to tuberculin which later becomes negative? In these parapsoriasis cases which may eventually turn into a fully-developed reticulosis the Mantoux reaction may become negative so late in the day it would not be of prognostic significance.

**Dr. Brian Russell:** I do not know of any evidence to show whether the allergy in Hodgkin's disease is primary or acquired. Hoyle did show that allergy is more common in Hodgkin's disease (20/43 patients) than in controls of the same age groups (9/43 patients).

POSTSCRIPT (17. 2. 56).—A.B.'s Mantoux reaction has been converted to positive at 1 in 100 but remains negative at 1 in 1,000.—B.R.

**Lymphocytic Infiltration of the Skin.**—C. D. CALNAN, M.B.

J. E., male, aged 40.

*History.*—Four years: eruption of red lumpy lesions on his back which looked like heat lumps. No irritation. They have occasionally cleared entirely but do not alter in pattern or appearance at all quickly.

*On examination.*—1952: Erythematous raised infiltrated lesions, arranged as papules or plaques or in rings. These are situated in the middle of the back with 2 similar lesions on the left upper arm. The colour is a bright pinkish red. No enlarged glands, liver or spleen found.

1955: Condition essentially unchanged but serial photographs confirm that the lesions are not fixed.

*Investigations.*—Blood count, E.S.R. and plasma proteins normal. No L.E. cells found. W.R. negative.

Histology: "The epidermis does not show any appreciable changes. The vascular network of the corium is enveloped in a thick mantle of round cells. The vessels themselves do not show any changes."

*Comment.*—I am showing this patient because I believe he is an example of a condition that has aroused interest recently in the United States. It occurs most frequently on the face but has been seen on the limbs and trunk. The differential diagnosis includes lupus erythematosus and its profundus type, polymorphic light eruption, chronic annular erythemas, sarcoid, reticuloses, and syphilides. Its distinguishing features are the reddish pink colour, absence of relation to light, failure to respond to chloroquine or X-rays and the lack of fixity of individual lesions. The histology is rather striking though not diagnostic.

These cases need to be followed to exclude a reticulosis and the criteria for diagnosis should be strict. But the condition at present would appear to be an entity separate from lupus erythematosus and the reticuloses.

**Dr. H. Haber:** The histology shows a very marked round cell infiltration involving vessels and appendages. The epidermis, however, is normal. This fact is against the diagnosis of lupus erythematosus. Otherwise the histology is not diagnostic for a single condition. It may occur in Darier's erythema annulare, it may be seen in "-ide" eruptions due to trichophyton infection. Perhaps one could include these cases in the large group of benign lymphadenosis of the skin as described by Bäfverstedt (1943, *Acta derm.-venereol., Stockh.*, **24**, Suppl. 11).

**Scirrhous Metastasis Simulating Necrobiosis Lipoidica.**—R. G. HOWELL, M.R.C.P. (for G. B. MITCHELL-HEGGS, O.B.E., F.R.C.P.).

Mrs. E. V., aged 49.

1952: Right radical mastectomy and radiotherapy for scirrhous carcinoma with axillary gland involvement.

June 1954: She developed a patchy scarring alopecia gradually coalescing to form large plaques at the frontal region and vertex.

July 1955: Similar plaques appeared in the skin of the back.

September 1955: She complained of diplopia for long distance.

*On examination.*—There were large areas of alopecia at the frontal area and vertex, where the scalp was atrophic, fixed to the underlying tissue, with central depression and slightly raised edges (Fig. 1). The colour was yellow-brown, and there was much telangectasia. There were 4 to 5 similar plaques in the skin of the back. There was mild nystagmus of the abducting eye on looking to the right.

*Investigations.*—X-ray of the skull, chest and spine and long bones showed no evidence of metastases.

*Glucose tolerance curve:* Fasting blood sugar 110 mg./100 ml.; 45 min. after glucose 195, 90 min. after glucose 150, 120 min. after glucose 125 mg./100 ml.

*Biopsy* of plaques on scalp and back showed hyalization of collagen, with narrow bands of cells between the collagen bundles, consisting of fibroblasts and chains of small irregular metachromatic carcinoma cells.

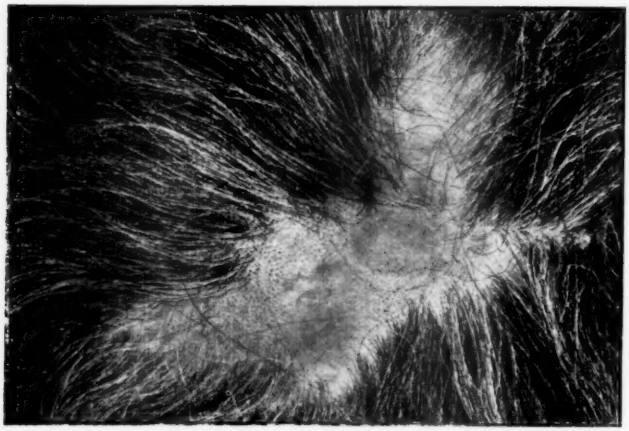

FIG. 1.—Atrophic plaque at the vertex.

**Dr. H. Haber:** The histology shows the characteristic appearance of a scirrhous carcinoma. The tissue spaces of the collagen are permeated by rows of cells of polygonal shape and hyperchromatic nuclei. The bundles of the collagen themselves show thickening and hyaline degeneration. The latter fact gives the skin the appearance of morphœa. A similar feature is to be seen in the morphœa type of basal cell epithelioma (Figs. 2 and 3).

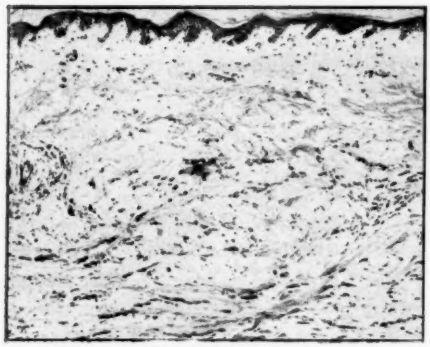

Fig. 2.—×113.

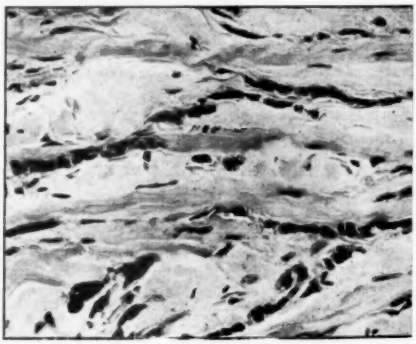

Fig. 3.—×485.

The following cases were also shown:

**Keratosis Punctata Resembling Pityriasis Rubra Pilaris.**—Dr. J. E. M. WIGLEY and Dr. D. L. REES.

**Cutis Laxa with Urticaria and Purpura.**—Dr. R. P. WARIN.

**"Erythroplasia" Associated with Multiple Intra-epidermal Carcinomata.**—Dr. M. GARRETTS (for Dr. W. N. GOLDSMITH).

**Melanodermatitis Toxica Lichenoides.**—Dr. H. T. H. WILSON.

**Purpura Telangiectodes Majocchi or Schamberg's Progressive Pigmentary Dermatosis.**—Dr. THERESA KINDLER.

**Case for Diagnosis. ? Pityriasis Rubra Pilaris.**—Dr. C. M. RIDLEY (for Dr. J. S. PEGUM).

**Lichen Planus with Nail Dystrophy.**—Dr. R. H. MARTEN (for Dr. D. I. WILLIAMS).

# Section of Psychiatry

President—W. D. NICOL, M.B., F.R.C.P.

[*October* 11, 1955]

## General Paralysis of the Insane [*Abstract*[1]]

"Give me the power to produce fever, and I will cure all diseases"—*Hippocrates*

### PRESIDENT'S ADDRESS

By W. D. NICOL, M.B., F.R.C.P.

To British psychiatry belongs the credit of the first clinical description of general paralysis of the insane (G.P.I.) as a separate entity. John Haslam, surgeon-apothecary to Bethlem, wrote an account of a man aged 42, who was admitted in June 1795, and died in August 1796, in which he gave a description of the classical grandiose type. It was not till 115 years later that general paralysis was proved to be an organic disease of the brain caused by syphilis.

The first serious attempt to treat this disease by chemotherapy was made with a trivalent arsenical compound (606) discovered by Ehrlich in 1910, but Mott (1915) offered little hope of its cure. "I have come to the conclusion that those late degenerative forms of syphilis of the nervous system (and I refer especially to general paralysis), have not been cured, nor even greatly benefited, by any treatment with salvarsan or neosalvarsan, whether administered intravenously or intrathecally." He concluded that "we must rather look to the prevention of the spread of syphilis, and its early diagnosis and treatment by modern methods, as the most hopeful way of combating this terrible malady".

The synthesis of a pentavalent arsenical, tryparsamide, in 1919 offered a new hope to sufferers from general paralysis. It was found that patients improved physically and remissions were obtained in about 30%; but it had one great disadvantage—its comparatively infrequent but very serious toxic effect on the optic nerve.

Fever therapy opened up a new era of treatment. We are indebted to Bruetsch (1946) for the translation of an unpublished monograph on "The History of the Malaria Treatment of General Paralysis" by Wagner Jauregg. The rationale of malaria therapy was based on the observation that psychotics, following an intercurrent feverish illness, occasionally showed great improvement. In 1887, Wagner Jauregg, while claiming no originality for his proposal, put forward the idea of intentionally inducing a febrile disease, suggesting malaria or erysipelas, as a therapeutic method. He selected the streptococcus of erysipelas as the lesser of the two risks, but this proved entirely unsatisfactory. In 1890, with the appearance of Robert Koch's tuberculin, Wagner Jauregg began treating patients with this at the Psychiatric Clinic at Graz in Austria. After a four-year trial of tuberculin injections alone, he combined these with mercury injections, because, as he said, "I never could convince myself that specific antisyphilitic treatment of general paralysis was without

[1] This paper will appear in full in the *British Journal of Venereal Diseases*.

any value whatsoever, a view held by most psychiatrists of that period". Although with the combined tuberculin-mercury therapy complete remissions were obtained, relapses were frequent. In an attempt to improve on this, he tried various vaccines, finally selecting typhoid vaccine as the most reliable fever-producing agent, and replacing mercury by the recently introduced salvarsan. It was not till thirty years later, in 1917, that Wagner Jauregg returned to his previous idea of malaria therapy. At that time infective material was abundant in soldiers returning from the Balkan front: hospitals were full of wounded personnel and by accident a minor casualty suffering from malaria had been admitted to one of Wagner Jauregg's wards. "This I regarded as a sign of destiny." On that day (June 14, 1917) three general paralytic patients were inoculated by rubbing a few drops of the soldier's blood into several superficial scarifications of the skin. The favourable reports of his method of treatment were, at first, received sceptically by colleagues and other workers, but later, clinicians in Vienna and elsewhere on the Continent hailed the new discovery, and in 1927 Wagner Jauregg was awarded the Nobel Prize for his work.

British psychiatry was conservative and reluctant to give this new treatment a trial and it was not until July 1922 that the first general paralytic was inoculated with malaria in this country at Whittingham Mental Hospital by Dr. R. M. Clark. Cases continued to be infected somewhat sporadically during the next three years until 1925, when the Malaria Therapy Centre (now the Mott Clinic) was established at Horton Hospital, Epsom, from which infective material is supplied to hospitals all over the British Isles and as far afield as the Continent. It has been my good fortune to be associated with this Centre since its inception by the late Colonel S. P. James, F.R.S., and Mr. P. G. Shute.

The changed outlook on this hitherto fatal disease stimulated research throughout Europe and the United States with the production of a spate of literature. There were difficulties in the appraisal of this new therapeutic measure, as in most clinics malaria was supplemented either by trivalent or pentavalent arsenicals. At Horton, for the first seven years, malaria alone was employed. The immediate results compared favourably with other clinics where malaria was supplemented with chemotherapy: life was prolonged, the physical condition of the patient was greatly improved, roughly one-third of the patients were discharged from mental hospitals.

It is of interest to record that the advent of malaria therapy gave a great stimulus to the study of malaria by the malariologist. For the first time an opportunity had been given to study malarial infection as an experimentally-produced condition: never before had it been possible to observe the clinical course of the disease in the primary attack. Much work was done on prophylaxis and testing out new synthetic antimalarial drugs. We may well claim that psychiatry had made a valuable contribution to another branch of medicine and the discoveries have exercised far-reaching effects in the field and in the epidemiology of malaria.

Penicillin is the third revolutionary advance in the treatment of syphilis in this century and has the unique characteristic of being efficacious at all stages of the disease and in all its manifestations.

It is curious that the two most successful therapeutic agents in G.P.I.—malaria and penicillin—should act in totally different ways. Although *T. pallidum* is susceptible to heat, neither Wagner Jauregg nor many other later observers believed that the efficacy of malaria was entirely due to the temperature reaction. Bruetsch (1949) maintains that the principal therapeutic factor is the activation of the reticulo-endothelial system, leading to the production and stimulation of macrophages and the development of immune reactions, thereby inhibiting the treponemata. Hence the action of malaria is indirect and relatively slow. Penicillin, on the other hand, is a powerful spirochæticidal agent and acts directly and rapidly.

Since the advent of the penicillin treatment of neurosyphilis, the Herxheimer reaction, long familiar to the venereologist, has appeared in the field of the neurologist and psychiatrist. The figures of the incidence of the reaction are extremely variable; at the Mott Clinic we have been fortunate and our numbers up to the present time have been extremely low.

Reports of severe and even fatal anaphylactic reactions to penicillin have been appearing in the literature. In view of this, the recommendation has been put forward that, prior to administration, patients should be investigated for penicillin sensitivity, and where this is found or is suspected, the drug should be withheld.

There is no doubt that the employment of penicillin is remarkably successful in the treatment of some cases. Many penicillin failures reported in the early days were probably due to inadequate dosage: the generally accepted view nowadays is that at least 10 mega units should be given.

It is always interesting to speculate and sometimes profitable. In 1946 I analysed the results of a ten-year follow-up of two groups of 217 patients, treated respectively by malaria alone and malaria plus tryparsamide, and found decidedly better results, both clinically and serologically, in the combined-treatment group. The survival rates of the two series fully confirmed the superiority of malaria plus tryparsamide over malaria alone. The time is approaching when it will be possible to make a similar analysis of the results of a ten-year follow-up in two groups, treated respectively with penicillin alone and penicillin plus malaria.

In a personal communication, Sir Gordon Covell gave me the results of an investigation he had initiated in 1954 into the position of penicillin in the treatment of neurosyphilis. A questionnaire was circulated to various centres throughout the United States and Europe, in which the following questions were asked:

(1) What is the present trend in the incidence of neurosyphilis?
(2) To what extent are (*a*) penicillin, (*b*) malaria therapy, being used for the treatment of neurosyphilis?
(3) Are any figures available as to the proportion of cases treated with penicillin who have failed to respond to treatment or who have relapsed within a period of two years following treatment?
(4) Do you know of any evidence suggesting that the *S. pallida* is becoming resistant to penicillin?
(5) What is considered the choice of treatment for neurosyphilis?

The answers to two of the questions were unequivocal. It was the universal experience that the incidence of neurosyphilis, and especially general paralysis, had been steadily decreasing; and no evidence was forthcoming of the development of a penicillin-resistant strain of *T. pallidum*.

The replies to the other three questions were more indefinite. This may be an expression of the fall in incidence of general paralysis. In Canada the method of choice is penicillin plus malaria, although penicillin alone is largely used owing to the lack of available malaria; this is not usually considered sufficient and is often supplemented by tryparsamide. The replies from the United States vary — Bruetsch (Indianapolis) maintains that penicillin is probably adequate by itself; in Maryland and the Boston Psychopathic Institute malaria therapy is still used, but only in cases which have relapsed. On the other hand, Eldridge of the St. Elizabeth Hospital, Washington, thinks there is a decided risk of the ultimate development of a penicillin-resistant strain of *T. pallidum* and feels that penicillin alone is definitely inadequate.

In Europe the position seems to be somewhat different. There is a general consensus of opinion in Austria, Belgium, Czechoslovakia, France, Germany, Holland, Italy, Norway, Sweden and Switzerland, that the method of choice in general paralysis is combined treatment, malaria plus penicillin. The remaining two countries from which replies were received, Denmark and Russia, differ. In Denmark, patients are treated in the Kettering hypertherm and given penicillin, unless they are in mental hospitals when the treatment is penicillin alone. In Russia it is thought that fever therapy is only indicated in cases resistant to penicillin.

The general trend towards combined treatment—penicillin plus malaria—shown by the replies to the questionnaire, came as a considerable surprise since, up to the present, there is no indication in the literature of this apparent change. Penicillin has largely usurped the role played by malaria but my long experience of this disease leads me in the same direction: combined therapy is probably the method of choice, at any rate in parenchymatous neurosyphilis.

It is now universally accepted that repeated examinations of the spinal fluid at six-monthly intervals provide a useful guide in the evaluation of the therapy. In fact, patients with syphilis of the central nervous system should remain under observation for life.

In the United States, Dattner *et al.* (1952) have stressed the importance of fluid examination almost to the exclusion of the consideration of the clinical condition of the patient, and criticism has been levelled at the concept of what is referred to as "treating the spinal fluid and not the patient". In the course of their studies two conclusions were reached: (1) No significant clinical improvement can be expected from further antisyphilitic therapy in patients whose spinal fluid findings have indicated persistent inactivity of the syphilitic infection; further treatment of patients who continue to be psychotic must be directed against the psychosis and not against the *T. pallidum*, and (2) relapses of neurosyphilis, including general paresis, do not occur more than two years after treatment has produced spinal fluid findings which indicate an inactive process.

The clinical results of treatment of general paralysis are of considerable practical and theoretical interest.

Kral and Dörken (1953) carried out a comparative serological and psychological investigation on 52 institutionalized cases of dementia paralytica in the Verdun Protestant Hospital, Montreal. They found that the treated cases with negative spinal fluid showed a more pronounced deficit both of intelligence and of personality resources than those cases in an active phase. Clinically, this group of serological negative cases can be subdivided into groups, one where apparently no further progress of the paralytic process occurs, and a second group, where despite a permanently negative fluid, a slow but definite deterioration can be recognized. To explain this, the authors maintain that their results indicate that at least two pathogenic factors are at work—one connected with the acute inflammatory process and responsible for the clinical picture and the fluid abnormalities, and relatively easily influenced by penicillin or combined therapy; and another, long-acting, not influenced at all by therapy but responsible for progressive deterioration, even in the patient with a completely negative fluid. This second factor has been suggested by Merritt *et al.* (1937) to be of a vascular nature.

In the Mott Clinic at Horton, one of the most important aspects of the centre was the establishment of an adequate follow-up. This valuable work has been elaborated by Whelen and Bree, who in a recent communication (1954) investigated 132 cases of general paralysis and taboparesis, who were treated between the years of 1942 and 1946, and were subsequently discharged. 39 of this group made a complete recovery, 81 exhibited various degrees of improvement, 11 were stationary and 1 could not be classified. All the recoveries took place within three years at the maximum. In the "improved" group of 81, only 19 attained an optimal condition within three years, whereas 62 (77%) took longer. The patients who recovered did so apparently as the direct result of treatment, but in the improved group auxiliary factors, apart from adequate treatment, made an important contribution to their rehabilitation—a good prepsychotic personality, a dependable and sympathetic prop (the family, friends or even neighbours), and some kind of occupation, gainful or otherwise, that was within their capacity. The patients who came within the stationary group all lacked one or more of these factors.

In the Chief Medical Officer's Annual Report to the Minister of Health for 1953, certified deaths from G.P.I. were 91 men and 26 women: in 1911–1920, the average annual death-rate was 1,697 men and 383 women. The "clinic" figures for neurosyphilis for the last five years show little change, but many of these cases are asymptomatic.

With the marked decrease of general paralysis, one might well ask—Why devote so much time to its study in a special centre like the Mott Clinic? But syphilis has not yet been eliminated and until it has been, there will always remain that group of patients in whom the primary attack is so mild that it passes unnoticed, and those who, for one reason or another, have been inadequately treated. These people are always in danger of ultimately developing late manifestations of syphilis, somatic or nervous. Nor must we neglect the very important problem of contacts: some are detected in routine examination, others at antenatal clinics, or discovered in the investigation of families of patients suffering from general paralysis whether acquired or congenital. The incidence of venereal disease regularly rises during war, and indeed the last one was no exception as the following figures show.

In 1946 infections of acquired syphilis rose to 10,705 men and 6,970 women: in 1939 the figures were 3,574 and 1,412 respectively. The figures recorded do not include Service cases. If treatment for these primary attacks has been adequate, then late neuro recurrences will not be seen. Assuming that the average incubation period of general paralysis is ten to fifteen years, the next few years will give us the answer.

## REFERENCES


Bruetsch, W. L. (1946) *Amer. J. Psychiat.*, **102**, 577.

—— (1949) *J. Ind. dent. Ass.*, **42**, 211.

Dattner, W., Carmichael, D. M., De Mello, L., and Thomas, E. W. (1952) *Amer. J. Syph.*, **36**, 179.

Kral, V. A., and Dörken, H. (1953) *Amer. J. Psychiat.*, **109**, 684.

Merritt, H., Putnam, T. J., and Campbell, A. C. P. (1937) *Arch. Neurol. Psychiat., Chicago*, **37**, 75.

Mott, F. W. (1915) *J. ment. Sci.*, **61**, 175.

Nicol, W. D. (1946) *Brit. J. vener. Dis.*, **22**, 112.

Whelen, M., and Bree, M. H. (1954) *Lancet*, **i**, 70.

# Section of Neurology

President—Redvers Ironside, F.R.C.P.

[*December* 1, 1955]

## DISCUSSION ON THE NEUROLOGICAL COMPLICATIONS OF THE ACUTE SPECIFIC FEVERS

**Dr. Henry Miller:** The present account is based on a survey of the literature of para-exanthematous encephalitis and related syndromes published up to the end of 1953. This was carried out in Newcastle-upon-Tyne jointly with Dr. J. B. Stanton, now of the Department of Neurology, Edinburgh, and Dr. J. L. Gibbons, now at the Maudsley Hospital.

Our special interest in the subject arose from an attempt to evaluate the effects of ACTH and cortisone in cases of acute disseminated encephalomyelitis and related acute inflammatory diseases of the nervous system, and from our early realization as to how little reliable information is available about the natural history and prognosis of such cases. The reason is not far to seek. Even in a lifetime of clinical work as neurologist, pædiatrician, or specialist in infectious diseases, no more than a handful of these illnesses will be encountered, unless special steps are taken to search them out. Textbook generalizations are largely based on such fragmentary experience. But there is a more general reason for the absorbing interest of these cases. The encephalomyelitic and related illnesses which follow exanthemata are unusual amongst the acute demyelinating diseases in that the major ætiological agent is clearly evident. This does not apply, of course, to pathogenesis, the nature of which is still debatable.

The observations I shall describe are based on a comprehensive review of the available world literature in the case of measles, chickenpox and rubella, and on a somewhat less exhaustive but fairly complete study of the recorded neurological complications of mumps, whooping cough, and scarlet fever. The questions we set out to answer in reviewing this material may be summarized as follows: First, the actual incidence of neurological complications in the various fevers. We must admit at once that information on this point remains very sketchy. Secondly, we wished to find out if there is any difference in the proportional distribution and clinical characteristics of the various syndromes which follow each disease; and to study more closely any differential clinical features and their prognostic significance. Thirdly, we wished to study immediate and long-term prognosis, and the tendency to sequelæ. Fourthly, we wanted to find out whether the very variable spinal fluid changes encountered in this group of diseases were of any significance; and finally, to investigate the relation between duration of illness and histopathological findings recorded in fatal cases.

We have substantiated the close pathological and clinical similarities generally considered to exist between the neurological illnesses which follow measles, chickenpox, and rubella, and these are considered together in the first part of the paper. The second part presents briefly the neurological complications of the other diseases concerned, in each of which some complicating factor is present.

### Neurological Complications of Measles, Varicella, and Rubella

The literature in relation to neurological complications in measles is vast, and, since our figures are based on an analysis of more than 900 cases (at least 600 of which are recorded in some detail), our information about this group of cases is probably more reliable than that relating to the other infectious diseases. In the case of chickenpox, our figures are based on about 130 cases, while there are on record only 80 cases of neurological illness following rubella.

It can be said with some certainty that although a higher incidence of neurological complications has occasionally been observed—as in the virgin soil of south-west Greenland (Christensen *et al.*, 1953)—the incidence of measles encephalitis is in general a little less than one in a thousand of all cases. There are no similarly reliable figures available for the incidence of chickenpox encephalitis, but there is some suggestive evidence that encephalitis more rarely complicates rubella than either of the foregoing diseases.

In all three conditions, the vast majority of neurological complications are either frankly encephalitic or encephalomyelitic (encephalitis with associated myelitic or radicular lesions). In each instance a small minority is affected by an uncomplicated myelitis, or an uncomplicated polyradiculitis. The percentage distribution of these syndromes in each disease is shown in Table I. The fact that only the figures for measles are based on a large number of cases should be borne in mind, but the similarity of the general pattern is clear.

TABLE I.—NEUROLOGICAL COMPLICATIONS OF MEASLES, VARICELLA, AND RUBELLA: PERCENTAGE INCIDENCE OF CLINICAL SYNDROMES

| | Measles (911 cases) | Varicella (134 cases) | Rubella (80 cases) |
|---|---|---|---|
| Encephalomyelitis | 95 | 90 | 92 |
| Myelitis | 3 | 3 | 4 |
| Polyradiculitis | 2 | 7 | 4 |

TABLE II. — AVERAGE LATENT PERIODS IN DAYS OF NEUROLOGICAL COMPLICATIONS FOLLOWING MEASLES, VARICELLA, AND RUBELLA

| Measles (616 cases) | Varicella (95 cases) | Rubella (75 cases) |
|---|---|---|
| 4·7 | 6·3 | 3·8 |
| 5·5 | 8·25 | 6·7 |
| 9 | 11·25 | 8·7 |

The close similarity seen in the distribution of these syndromes as amongst the three diseases is paralleled by the relation which exists between the latent periods of the various syndromes occurring in each disease. By this I mean the interval elapsing between the appearance of the rash and the development of the neurological complication (Table II).

In each disease polyradiculitis has an average latent period twice as long as that of encephalitis, and in each instance myelitis occupies an intermediate position. These latent intervals vary as do the incubation periods of the three exanthemata themselves.

Occasionally encephalitis precedes the appearance of the rash, and its nature becomes clear only with the development of the exanthem. This occurs most commonly—in no less than 8% of cases—in rubella, which has the shortest latent period. No instance of pre-exanthematous myelitis or polyradiculitis has been recorded in association with any of these diseases.

*Measles Encephalitis*

Our knowledge of measles encephalitis is based on a study of a large number of case-histories.

Measles encephalitis usually begins four to five days after the appearance of the rash. There is no correlation between the severity of the exanthem and the occurrence of encephalitis, which has several times been reported after the mild illness which follows attenuating doses of γ-globulin. Nor is there any convincing evidence of a consistently inverse relationship between the severity of the rash and the occurrence of neurological complications, a suggestion on which some Continental writers have based theories of pathogenesis. Measles encephalitis shows no predilection for either sex, but the mortality in female patients is 50% higher than in males. There can be no doubt that the condition tends to affect predominantly older victims of the exanthem: at any rate 23% of all recorded cases of measles encephalitis occurred over the age of 10 years, as compared with an incidence of less than 4% of cases of measles above this age in the British Isles.

The two commonest modes of onset are by the abrupt development of convulsions followed by coma, or by a slow lapse into stupor following a few hours of headache, vomiting and restlessness. Coma occurs in 45%, stupor in about 25%, and in the remainder drowsiness of some degree is almost invariable. Fever is usual. Meningism and convulsions each affect half the cases. The clinical picture is polymorphic, and there is no neurological sign that has not been encountered. Hemiplegia, tetraplegia, ataxia, retention of urine, optic neuritis, paralysis of cranial nerves, and involuntary movements of various types are all common findings.

No instance of relapse or recurrence of measles encephalitis has ever been reported. This is in contrast with the not infrequent recurrence encountered in encephalomyelitis following banal infections. The mortality of measles encephalitis is about 20%. When death occurs it usually does so within the first three days of the illness, and scarcely ever later than a week after the onset. The degree of recovery which can occur even where there have been striking initial signs of massive brain damage is remarkable, and more than 80% of the patients who survive show no disability by the end of six weeks. The spinal fluid may be normal throughout, but often shows a lymphocytic pleocytosis, with a normal or very slightly raised protein level. The spinal fluid findings are unrelated to clinical

severity, they have no prognostic significance, and more surprisingly still, they bear little or no relation to the presence or absence of meningism.

Astonishingly few neurological signs remain in recovering patients. Indeed, except for an occasional residual hemiplegia, or paraplegia, sequelæ are more often psychiatric than neurological. Both types of sequelæ are commoner in young patients who have had severe illnesses characterized by coma and convulsions. Both major and minor neurological symptoms tend to improve during long-term follow-up. Probably the most important occasional sequela is intellectual defect. This represents the result of severe generalized cerebral damage, minor degrees of which are often manifest in the form of more transient nervousness or behaviour disturbances. The occurrence of intellectual defect after measles encephalitis seems to be limited to young children, and no case has been reported in an adult. Some of these children show an immediate psychological deficit, others merely a failure of development, with a falling intelligence quotient over the years. Although the disease appears to be appreciably more fatal over the age of 16, the incidence of sequelæ is less in the older patients.

An analysis of symptoms in relation to mortality shows that coma and convulsions are unfavourable prognostic features, each of which is associated with an increase of mortality; 38% of patients who became comatose died, as compared with a 14% mortality in cases without coma, while in patients who convulsed, the mortality was just over 30%.

A point of some interest arises in connexion with hemiplegia. When hemiplegia occurs as a feature of an encephalitic illness the illness is severe and has a considerable mortality, but in surviving cases, good recovery of function is common. In some instances, however, a sudden hemiplegia follows measles in the absence of any other evidence of encephalitis, and though all such recorded cases have survived, the hemiplegia is permanent in the large majority. Pathological evidence suggests that in the first group the hemiplegia may arise on the basis of a largely reversible, generalized, and even symmetrical demyelinating lesion. In the group of isolated hemiplegias, however, both the history of onset and the poor recovery suggest the occurrence of a major vascular accident.

*Pathological findings.*—From reports of 44 adequately recorded fatal cases of measles encephalitis we have been able to plot the histopathological findings against the duration of symptoms before death, in the hope of revealing something of the march of pathological events in the brain during the course of the illness. We may say at once that our observations support the view originally put forward by Brain, Hunter and Turnbull (1929) that the appearances of acute disseminated encephalomyelitis represent stages in the development of a single pathological process beginning with congestion and œdema, and ending with the fully developed picture of perivenous infiltration and demyelination. In this, as in other diseases, histopathological findings cannot be rigidly correlated either with severity or duration of clinical symptoms. For instance, in one case dying within twelve hours of the apparent onset, autopsy revealed massive perivenous infiltration and demyelination which clearly indicated that the pathological process must have been far advanced before the clinical onset. On the whole, however, the gradation of changes in these 44 cases, dying after periods varying from twelve hours to eight months after the onset of their encephalitic illnesses, indicates a fairly well-defined natural history. The initial change in the brain appears to be congestion, followed within a matter of hours by mural infiltration of the smaller venules chiefly with mononuclear cells, and then by the development of perivenous œdema and occasional hæmorrhages of similar distribution. In some fulminating cases the intensity of these changes leads to death from cerebral purpura. In progressive cases, however, perivenous infiltration with microglial and lymphocytic cells is seen, and demyelination follows in the same regions. Such changes may be conspicuous within forty-eight hours of the onset. The removal of fat by scavenging phagocytes ensues some days later, and leaves demyelinated areas which may appear confluent in the course of time. Nerve-cell changes vary in prominence but are by no means invariable. Direct involvement of blood vessels is a frequent if not invariable change, and may vary from lymphocytic infiltration of the vessel wall to actual vascular necrosis. At some stage all these changes are completely reversible. In other recorded instances, demyelinated areas have remained for several years, unassociated with progressive extension or with extending gliosis.

*Measles myelitis.*—The literature contains reports of 24 cases of myelitis complicating measles, 18 transverse and 6 ascending. 6 patients became tetraplegic, 4 showed bulbar palsy, 1 bilateral optic neuritis. Meningism occurred in 12. In each instance the lesion progressed for a few days but recovery usually began in as many weeks. Severe disability usually cleared within six weeks, with extremes of fourteen days and three years. 5 cases died, after illnesses averaging nine days in duration. 12 patients recovered completely, 2 were left with severe paraplegia. Others had some residual disabilities, usually minor. Again spinal fluid changes were variable and insignificant. Pathological reports are scanty

and there is uncertainty as to the respective roles of diffuse demyelinating processes and focal vascular occlusion (e.g. segmental thrombosis of the anterior spinal artery, possibly on an arteritic basis).

It should be noted that while the mortality in this small group of cases of myelitis is similar to that encountered in measles encephalitis, remarkable recovery of function is the rule in all but the severest cases.

*Polyradiculitis complicating measles.*—10 cases are on record, 8 being males. Cranial nerve involvement was common: 9 showed bulbar symptoms, 7 facial palsy (5 bilateral), and 4 ophthalmoplegias. One case had coincident encephalitis, 3 had meningism. Motor weakness was more conspicuous than sensory impairment. All cases recovered, but some suffered residual focal muscle wasting and weakness. A marked rise in spinal fluid protein was invariable and 4 cases showed a classical albumino-cytological dissociation.

*Varicella and Rubella*

How far are the encephalitic illnesses which occasionally complicate chickenpox and rubella identical with or similar to measles encephalitis? Briefly, the clinical and pathological similarities between the members of this group are so much more striking than their differences that it is impossible to escape the conclusion that they represent manifestations of closely-related pathological processes. Nevertheless, certain clinical differences are unequivocal.

As with measles, rubella encephalitis affects both sexes equally and has a higher mortality amongst females. Varicella encephalitis, however, is twice as common, and appreciably more fatal, amongst males. Such evidence as is available suggests that in each instance older subjects of these exanthemata are more liable to develop encephalitis. Reliable evidence as to the age incidence of the exanthemata is surprisingly scanty but the fact that rubella encephalitis tends to occur at a later age than the other two (31% of recorded patients were over the age of 16) is almost certainly related to the later age incidence of the exanthem itself.

The generally accepted view that rubella encephalitis is especially rare finds some support from such figures as are available: not so the view that it is also benign. Like that of measles encephalitis its mortality is in the region of 20% as compared with 10% for varicella. The greater mildness of the latter is further illustrated by the observation that whereas the mortality of measles encephalitis below the age of 5 is over 30%, no fatal case of varicella encephalitis below this age has been recorded.

*Clinical features.*

The picture in all these forms is polymorphic and they all follow the same general pattern. There is no neurological symptom or sign that may not be encountered, and no feature which is pathognomonic of one of these forms of encephalitis as opposed to the others. In fact, in the absence of a clear history of the exanthem it would be quite impossible to differentiate the neurological illnesses. While varicella encephalitis is in general a milder disease, there are occasional cases following chickenpox which are more severe than the majority of instances of post-measles or post-rubella encephalitis. Furthermore, there are some symptoms, frequent enough to permit reasonably accurate assessment, in which there is no apparent difference of incidence between the three conditions. Involuntary movements for instance are seen in between 15 and 20% of all cases, and muscular hypotonia is somewhere between 20 and 30%. The major difference, however, which we believe to be related to the undoubtedly better prognosis of the varicella cases, is in the incidence of coma, convulsions, and extensor plantar responses, and is illustrated in Table III.

TABLE III.—POST-EXANTHEMATOUS ENCEPHALITIS: PERCENTAGE INCIDENCE OF CLINICAL FEATURES

| | Measles | Rubella | Varicella |
|---|---|---|---|
| Coma .. .. | 45 | 52 | 19 |
| Convulsions .. | 45 | 57 | 19 |
| Hemiplegia .. .. | 12 | 7 | 3 |
| Extensor plantar(s) | 71 | 66 | 28 |
| Ataxia .. .. | 10 | 13 | 34 |
| Nystagmus .. .. | 10 | 10 | 21 |
| Mortality .. .. | 20 | 20 | 10 |

Only 19% of cases of varicella encephalitis became comatose, as opposed to 45% in measles and 52% in rubella. The mortality in comatose cases was in fact slightly higher in varicella than in the other two forms of encephalitis, and the difference in mortality is probably related in part at any rate to the finding that fewer cases of varicella encephalitis did in fact become comatose. The figures in the case of convulsions are almost identical, and

their implications similar. Hemiplegia was seen in 12% of cases of measles encephalitis, and in 7% of the rubella cases, with a figure of only 3% for varicella. Similar figures for the incidence of unilateral or bilateral extensor responses are 71% (measles), 66% (rubella), and 28% (varicella). The presence of extensor responses is an unfavourable prognostic feature, usually indicating widespread or massive lesions, and often associated with coma. When, however, we come to the incidence of symptoms indicating cerebellar disturbance, the position is reversed; ataxia and nystagmus are respectively three times and twice as common in chickenpox encephalitis as in encephalitis complicating either of the other two diseases under discussion.

These findings bear out to a considerable extent traditional clinical observations not so far as we know previously subject to numerical analysis. It should be noted, however, that rubella encephalitis is certainly no less severe than that which follows measles and may indeed be a slightly more serious disease. In relation to myelitis and polyradiculitis, the figures are small but again the prognosis for these complications of varicella appears to be more favourable than in the case of the other two diseases.

*Sequelæ.*—The position is obscured by the much larger number of cases of measles encephalitis on record. There can be no doubt, however, that in all these diseases important sequelæ are rare in older patients, and that the disease is more prone to leave a permanent mark on the more vulnerable brain of the infant or young child. Under these circumstances the low incidence of sequelæ noted after rubella, the higher incidence after measles, and the intermediate position apparently occupied by varicella encephalitis, may be functions of their age-distribution rather than an index of the severity of the pathological process concerned.

*Histopathological appearances.*—The autopsy reports which are available on 7 cases of varicella encephalitis fully support the view that the pathological changes encountered are entirely similar to those seen after measles, though probably tending to be somewhat less severe. The pathological findings in relation to rubella are rendered not quite comparable by the remarkable and possibly significant fact that, despite the relatively high mortality of the condition, all the fatal cases on record have died within seventy-two hours of the onset of symptoms. The total of 15 fatal cases in the literature is small, but it is difficult to resist the implication that the brief duration of these fatal illnesses may be related to the short latent period in this form of encephalitis, to the considerable number of pre-exanthematous cases described, and to the high incidence of grave symptoms already noted. Such observations lend further support to the view that the relatively rare rubella encephalitis is an explosive illness, sometimes of great severity. The brief duration of the illness in the 9 autopsied cases on record also renders the pathological spectrum less complete than in the other two diseases, but the changes described are certainly compatible with the earlier stages of a perivenous demyelinating encephalitis, similar in its general histopathological as in its clinical pattern to that encountered in measles and varicella.

### Neurological Complications of Mumps, Scarlet Fever and Pertussis

The family resemblance which clearly exists between the neurological complications of measles, chickenpox, and rubella is less evident in relation to the nervous sequelæ of mumps, scarlet fever, and pertussis, in each of which instances complicating factors arise. In the case of mumps, the picture is obscured by the frequent occurrence of lymphocytic meningitis. In the case of scarlet fever many of the neurological complications encountered are secondary in the sense that they result from spread of streptococci by the blood stream, or arise on the basis of venous thrombophlebitis or nephrogenic hypertension. The case of pertussis, furthermore, appears to be unique both in the nature of the clinical syndromes encountered and in the histopathological findings recorded.

i) *Mumps*

The commonest neurological complication of mumps is a short-lived, benign and almost invariably recoverable form of lymphocytic meningitis usually appearing within a few days of the parotitis. There is some evidence that this condition is due to invasion of the meninges by the potentially neurotropic virus of epidemic parotitis, and this complication need not detain us further. It is, of course, possible that some cases of meningo-encephalitis complicating mumps may arise on a similar basis, as the result of spread of virus from the meninges to the brain. There is no certain pathological or experimental evidence that this actually occurs, but it is at least a possibility. Careful analysis of the more recent literature of mumps complications, however, provides strong evidence that sequelæ of the types already described in relation to measles do in fact occasionally occur in mumps; and that they have similar clinical features, prognosis, and histopathological findings. One important

feature, which leads us to believe (with Fanconi and others, 1945) that these complications are of the same nature as the neurological complications of measles, &c., already described, is that the spinal fluid findings in the cases which follow mumps are quite similar to those encountered in the three diseases already discussed, and, in particular, that mumps encephalitis may occur in the total absence of the meningism or the lymphoctyic pleocytosis which are cardinal features of mumps as of other forms of virus meningitis.

Our information about mumps encephalitis is based chiefly on 27 cases recorded since 1934. These illnesses began on an average seven days after the appearance of parotitis: the latent periods for encephalitis, myelitis, and polyradiculitis varied broadly as in the case of the three diseases previously described. Two-thirds of the encephalitic cases showed meningism, which is only a slightly larger proportion than in those following measles, &c. The mortality in the mumps cases was slightly more than 20%, coma again being an unfavourable feature, and there was little or nothing to distinguish this form of encephalitis from those already described. The amount of pathological material available is not great but all 5 adequately recorded cases reveal stages in the development of a perivenous demyelinating encephalitis similar to that more fully described in association with measles.

12 cases of mumps myelitis have been described and in 2 such cases (one of which had a coincident encephalitis), a diffuse demyelinating lesion was found in the cord. 6 cases of polyradiculitis following mumps are to be found in the recent literature. Again, these show no special features, but it is interesting to note a French report (Lamache and Dutrey, 1935) of 3 cases of polyradiculitis preceding the appearance of parotitis by a few days. In all but one (pre-parotitic) instance the spinal-fluid protein was raised, and often strikingly so.

In summary, then, it seems likely that neurological complications similar to those of measles, chickenpox, and rubella occur after mumps, though less frequently than and not necessarily in association with, the classical complication of lymphocytic meningitis.

ii) *Scarlet Fever*

The neurological complications of scarlet fever present a confused picture. In general, their incidence appears to be higher than those of any other exanthem, but the figures given (which vary from 1 : 800 to 1 : 300) include such diverse and non-specific conditions as hypertensive encephalopathy and vascular accidents complicating nephritis, septic meningitis, cerebral thrombophlebitis, and otitic hydrocephalus. If, however, the neurological disorders palpably due to complications of scarlet fever are excluded, we are left with a collection of cases of aseptic meningitis, encephalitis, myelitis, and polyradiculitis or polyneuritis.

*Aseptic meningitis.*—Lymphocytic meningitis, apparently unrelated to otitis or sinus thrombosis, is a neurological complication of scarlet fever with an incidence almost certainly higher for instance than that of encephalitis in measles. Analysis of 46 adequately reported cases reveals a remarkably consistent syndrome, beginning five to seven days after the onset of the exanthem, and apparently unrelated to its severity. The condition is characterized by fever, meningism, a paucity of focal neurological signs, a high lymphocytic pleocytosis in the spinal fluid and invariable recovery within a matter of days. This is, of course, the typical picture of benign lymphocytic meningitis: however, virus studies have so far proved negative, nor has serum administration been an invariable feature of these cases. Their ætiology remains obscure, but it should be borne in mind that a lymphocytic effusion is a non-specific reaction of serous membranes, the commonest response of the meninges to a wide variety of injurious agents of every type, and does not invariably bespeak virus invasion.

*Encephalitis.*—This is a much less common complication of scarlet fever, of which we have found 22 convincing cases in the literature. Most cases begin within the first week of the exanthem but a group were, much later, yielding an average latent period of eight to nine days. Clinically there was nothing to distinguish these illnesses from the encephalitides of measles, &c. 3 of this small group of cases died, which, as far as it goes, suggests the possibility of a mortality more comparable with that of varicella than with the other forms of encephalitis already discussed. Pathological findings are too scanty to permit generalization.

*Myelitis and polyradiculitis.*—2 cases of myelitis and 6 of polyradiculitis are on record. Like the encephalitis just described, these syndromes showed no clinical features which could be used to distinguish them from the similar complications of the exanthemata discussed.

iii) *Pertussis*

The neurological complications of pertussis differ both clinically and pathologically from all the post-infective disorders so far described—a statement which is made without prejudice to questions of ætiology or pathogenesis.

The only common neurological complications of pertussis are cerebral—in fact neither myelitis nor polyradiculitis has ever been fully authenticated. Pertussis encephalopathy is essentially a disease of early childhood. Cases are most often encountered during the first year of life while only 5 of 123 adequately recorded cases occurred over the age of 5 years—a feature which at once distinguishes the condition from post-exanthematous perivenous demyelinating encephalomyelitis, with its predilection for the older patient. The very variable figures given for the incidence of encephalopathy (less than 1% to 14%) may well have a semantic basis; most observers do not consider that the occurrence of an isolated convulsion in a child with pertussis demands a diagnosis of encephalopathy. Three-quarters of these 123 cases occurred between the second and fourth weeks of the illness, occasional cases in the pre-paroxysmal catarrhal phase. The illness is remarkably stereotyped, and almost invariably characterized by the sudden onset of convulsions (90%), which are most often generalized, and coma (84%), lasting for hours or days, with motor signs which are usually symmetrical, and bilateral extensor plantar responses. Of focal signs, hemiplegia is the commonest (possibly affecting about 1 in 5 patients), aphasia and monoplegia less frequent. Other focal signs are quite exceptional, and when they do occur probably tend to do so in older children. The onset of neurological signs in the fully conscious patient is very exceptional. Decerebrate rigidity due to virtual decortication, and organic psychoses have occurred. The spinal fluid is usually normal. The mortality is high, being at least 1 in 3, and in some series more than twice this figure; it is distinctly higher under the age of 2, and appears to have been unaffected by the employment of antibiotics. Sequelæ probably occur in about a third of all cases (i.e. nearly half the survivors): mental retardation, epilepsy, and spastic pareses (especially hemiplegia) being commonest.

Pathological changes in fatal cases may be surprisingly inconspicuous. The changes of perivenous demyelinating encephalitis have never been convincingly demonstrated, while massive cerebral hæmorrhage, air embolism, and tetany have been discarded as pathogenetic hypotheses. The most frequently encountered histopathological change is eosinophilic degeneration, most marked in the pyramidal cells of the hippocampus and the Purkinje cells of the cerebellum: this change is widely considered to be of anoxic origin. The condition may probably, for the present at any rate, best be regarded as an acute vascular encephalopathy possibly with an anoxic basis. The clinical similarity of these syndromes to those which occasionally complicate immunization with (sterile) pertussis antigen has been stressed, and suggests the possibility of an origin in some toxic effect whether or not a sensitization phenomenon.

## Summary and Conclusions

The triad of encephalitis, myelitis, and polyradiculitis represents the characteristic neurological complication of measles, varicella, and rubella. Mixed and intermediate syndromes—for example myelitis followed by encephalitis, or encephalitis accompanied by focal muscle wasting due to a radicular lesion—are sufficiently frequent to suggest a common pathogenesis for this group of complications. Histopathological evidence also appears to favour their origin in an acute inflammatory neuraxitis, varying in acuteness, intensity, and local incidence, but based essentially on an exudative, hæmorrhagic, and infiltrative process originating in the vascular tree of the nervous system. The perivenous demyelination which characterizes classical or fully-developed acute disseminated encephalomyelitis appears to be essentially secondary to the initial vascular insult. A syndrome clinically and pathologically similar is occasionally encountered in mumps, and possibly also after scarlet fever, in each of which instance it tends to be overshadowed by the very much more frequent occurrence of benign lymphocytic meningitis. In the case of pertussis, however, the occurrence of such a lesion has never been substantiated, and the catastrophic cerebral illness characteristic of this disease is both clinically and pathologically distinct, arising on a basis which is possibly anoxic.

What is the nature of the acute disseminated perivenous demyelinating encephalomyelitis which complicates these and other infectious diseases? Despite the minor clinical differences which we have shown to exist, for example, between the encephalitis of measles and that of chickenpox, these are surely much less striking than their similarities; while from the histopathological point of view I imagine that Dr. Blackwood will agree that on such grounds they cannot be distinguished one from another—or for that matter from the identical changes which may sometimes follow non-specific infections, Jennerian vaccination, or even serum sickness.

That such histopathological changes are due to invasion of the neuraxis by the causal virus of the initiating exanthem now appears highly improbable. Not only would it appear strange that the viruses of all these diseases, so widely different in all their other characteristics and activities, should all produce identical tissue reactions in the nervous system—but what of vaccination and serum sickness? Furthermore, the absence or inconspicuousness of neuronal damage in acute disseminated encephalomyelitis militates equally against the acceptance of the ingenious alternative hypothesis—that the initiating exanthem in some way activates an unidentified neurotropic virus already present in the tissues. Such a virus would need to be not only ubiquitous, but also quite unique in its pathogenetic properties.

The evidence for such a view cannot be adequately presented in a review of this kind, but there are many considerations both clinical and pathological which suggest the intervention of some common factor in pathogenesis between the specific initiating infection and the non-specific end-result in the nervous system, and that such a common factor may be anaphylactic sensitization. If this does prove to be the correct explanation, one influence determining variations in the clinical syndrome might well be the differing antigenic properties of the various infective agents. Such a possibility is suggested by the fairly consistent differences which are seen in the closely comparable neurological syndromes which may follow various types of prophylactic inoculation (Miller and Stanton, 1954).

## REFERENCES


Brain, W. R., Hunter, D., and Turnbull, H. M. (1929) *Lancet*, i, 221.

Christensen, P. E., Schmidt, H., Bang, H. O., Anderson, V., Jordal, R., and Jensen, O. (1953) *Acta med. scand.*, **144**, 430.

Fanconi, G., Zellweger, H., and Botsztejn, A. (1945) Die Poliomyelitis und ihre Grenzgebiete Basel.

Lamache and Dutrey (1935) *Bull. Soc. méd. Hôp. Paris*, 1770.

Miller, H. G., and Stanton, J. B. (1954) *Quart. J. Med.*, **23**, 1.


**Dr. W. Blackwood:** In considering this subject the clinician has great advantages, for he has numerous cases, whilst the pathologist appears to have had little opportunity of examining post-mortem material.

Table I has been compiled from my study, to date, of the literature. It indicates the great number of published clinical reports and the small number of post-mortem examinations. Only in the case of measles have we a satisfactory amount of material. I can only add one personal case to those listed and what I shall describe is certainly not the whole story of the pathology of the neurological complications of the acute specific fevers.

Table I.—Published Cases with Neurological Complications

| | Clinical reports | Post-mortem examinations |
|---|---|---|
| Mumps .. | Many with lymphocytic leptomeningitis | 12 |
| German measles | 39 | 7 |
| Chickenpox .. | 150 | 5 |
| Measles .. .. | >350 | >27 |

I shall confine my observations to whooping cough, mumps, scarlet fever, German measles, chickenpox and measles.

*Whooping cough.*—Neurological symptoms and signs are common. The post-mortem findings have been those of hæmorrhage, œdema and nerve cell degeneration. The nerve cells of the superficial layers of the cerebral cortex, of the striate body, hippocampus, the dentate nucleus and the Purkinje cells of the cerebellum are involved. These changes are considered by most authors to be mechanical in origin, associated with the upset of blood flow and with the cyanosis which accompany the paroxysms of coughing. Perivenous demyelination has not been reported.

*Mumps.*—There is commonly a lymphocytic leptomeningitis. In 3 cases a perivenous demyelinating encephalitis or encephalomyelitis has been reported.

*Scarlet fever.*—Pyogenic leptomeningitis, massive hæmorrhage, venous sinus thrombosis, and embolic softenings have been common post-mortem findings. Here again, however, there have been at least 2 cases reported with a perivenous encephalomyelitis.

*German measles.*—The pathological findings have been those of a perivenous encephalomyelitis. *In chickenpox*, where there are 5 post-mortem studies, and *in measles*, where we have at least 27 post-mortem studies, the picture has almost invariably been one of perivenous encephalomyelitis. There have been reports of solitary cases of acute hæmorrhagic leucoencephalitis complicating measles (Shallard and Latham, 1945) and chickenpox (Lander, 1955). In the latter case it must be noted that the patient was given chlortetracycline and streptomycin after he became comatose and paralysed. It is possible that these antibiotics influenced the pathological picture.

TABLE II

| | Whooping cough | Mumps | Scarlet fever | German measles | Chicken-pox | Measles |
|---|---|---|---|---|---|---|
| Hæmorrhage, œdema, nerve cell degeneration .. .. | + | | | | | |
| Lymphocytic leptomeningitis | | + | | | | |
| Pyogenic leptomeningitis, massive hæmorrhage, venous sinus thrombosis, embolic softening .. .. .. | | | + | | | |
| Perivenous demyelinating encephalomyelitis .. .. | | + | + | + + | + + | + + |
| Acute hæmorrhagic leuco-encephalitis.. .. .. | | | | | + | + |

Table II summarizes the post-mortem findings in the diseases under consideration. It can be seen that, with the exception of whooping cough, perivenous demyelinating encephalomyelitis has occurred in all of them, most frequently in German measles, chickenpox and measles. Acute hæmorrhagic leucoencephalitis has also been found in the last two conditions. As these two are the most important pathological findings, they will be considered in a little more detail.

(i) *Perivenous demyelinating encephalomyelitis.*—The distribution of the lesions is predominantly in the white matter of the cerebrum, cerebellum, brain-stem and spinal cord, although lesions in the grey matter are quite common in the basal ganglia and floor of the 4th ventricle. The lesions are related almost entirely to the small or medium-sized veins. The earliest change appears to be one of congestion and œdema of the walls of the veins and a very slight intra-adventitial infiltration by mononuclear cells and by polymorphonuclear leucocytes; and peri-adventitial infiltration by mononuclear cells. Demyelination does not appear to occur at this early stage.

The next stage is one which we commonly see and this can be illustrated by a personal case.

A little girl of 1 year 10 months was taken ill with slight fever, running eyes, nasal discharge and sore ears, also with slight discharge, during the course of a measles epidemic. This illness continued for seven days and then she started projectile vomiting, coma and convulsions, and died two days later. *Post mortem* (Edin. N.P.1498) the brain was very congested. The white matter throughout the cerebral hemispheres, mid-brain and pons and the grey matter of basal ganglia, mid-brain and pons showed the following features:

(1) Perivenous demyelination, with a variable degree of damage to the axons.
(2) A narrow intra-adventitial sleeve of inflammatory cells.
(3) A broad zone of less densely packed extra-adventitial cells, the majority of which appear to be of a phagocytic nature.
(4) Survival of nerve cells even within inflamed regions.

In sections stained by the Weigert-Pal technique the central vein is surrounded by a zone of demyelination. The normal myelin stains black and disintegration products of myelin also staining black are visible in phagocytes. Sections stained with Scharlach R hæmatoxylin show that many of the breakdown products of myelin are sudanophilic and are undergoing phagocytosis. Sections stained with hæmatoxylin and eosin show the loosely packed extra-adventitial cells and the narrow intra-adventitial sleeve of inflammatory cells which include small mononuclear cells, large mononuclear cells, occasional plasma cells, neutrophil leucocytes and sometimes eosinophil leucocytes. In this case there was an unusually large number of eosinophil leucocytes in the adventitial spaces.

(ii) *Acute hæmorrhagic leucoencephalitis.*—The post-mortem findings are essentially similar to those found in cases of acute hæmorrhagic leucoencephalitis which are preceded by respiratory infection. The lesions consist of multiple ring, ball and sleeve-like hæmorrhages related principally to capillaries and venules. The walls of these vessels have undergone fibrinoid necrosis. Fibrin extends into the perivascular spaces and even into

the adjacent nervous tissue, which is necrotic and infiltrated by neutrophil polymorphonuclear leucocytes.

There are only two cases of acute hæmorrhagic leucoencephalitis following exanthemata published during the last ten years. There are, however, reports in the older literature of cases with hæmorrhage and it is possible that some of these were acute hæmorrhagic leucoencephalitis. With the increased number of neurological centres in this country more of these cases may be identified and investigated.

A knowledge of whether both perivenous demyelinating encephalomyelitis and acute hæmorrhagic leucoencephalitis are to be considered as common types of post-infectious encephalitis is a matter of considerable interest and importance, especially in view of the hypothesis, recently supported by Professor Dorothy Russell, that these two conditions are variants of one pathological process.

There are histological similarities between the post-exanthematous lesions and those which are considered by many to be due to allergy. But similarity of appearance does not necessarily mean similarity of pathogenesis. The histopathological evidence is as yet too slender for any final conclusion to be reached as to whether allergy does or does not play a part in the pathogenesis of post-exanthematous encephalomyelitis.

I am indebted to Dr. A. F. J. Maloney and Mr. J. C. Sommerville of Edinburgh for assisting me with the re-examination of the personal case.

## BIBLIOGRAPHY

ADAMS, R. D., and KUBIK, C. S. (1952) *Amer. J. Med.*, **12**, 510.
VAN BOGAERT, L. (1933) *Rev. neurol.*, **59**, 150.
—— (1949) *Acta neurol. belg.*, **49**, 811.
DAGNELIE, J., DUBOIS, R., FONTEYNE, P., LEY, R.-A., MEUNIER, M., and VAN BOGAERT, L. (1932) *J. Neurol., Brux.*, **32**, 549.
DOLGOPOL, V. B. (1941) *Arch. Neurol. Psychiat., Chicago*, **46**, 477.
DONOGHUE, W. L. (1941) *J. Pediat.*, **19**, 42.
FAUST, O. A. (1938) *Arch. Pediat.*, **55**, 29.
FERRARO, A. (1944) *J. Neuropath.*, **3**, 239.
——, and SCHAFFER, I. H. (1931) *Arch. Neurol. Psychiat., Chicago*, **25**, 748.
FINLEY, K. H. (1937) *Arch. Neurol. Psychiat., Chicago*, **37**, 505.
—— (1938) *Arch. Neurol. Psychiat., Chicago*, **39**, 1047.
FORD, F. R. (1928) *Bull. Johns Hopk. Hosp.*, **43**, 140.
GREENFIELD, J. G. (1929) *Brain*, **52**, 171.
LANDER, H. (1955) *J. Path. Bact.*, **70**, 157.
LHERMITTE, F. (1951) Les Leuco-encéphalites. Paris.
LITVAK, A. M., GIBEL, H., ROSENTHAL, S. E., and ROSENBLATT, P. (1948) *J. Pediat.*, **32**, 357.
NELSON, R. L. (1939) *J. Pediat.*, **14**, 39.
RUSSELL, D. S. (1955) *Brain*, **78**, 369.
SHALLARD, B., and LATHAM, O. (1945) *Med. J. Aust.*, i, 145.
TURNBULL, H. M. (1928) *Brit. med. J.*, ii, 331.
——, and MCINTOSH, J. (1926) *Brit. J. exp. Path.*, **7**, 181.

## DISCUSSION ON EXPERIMENTAL ALLERGIC ENCEPHALITIS

**Dr. C. E. Lumsden** (Sir Henry Head Research Fellow, The Royal Society)[1]: Brain tissue from many, and perhaps most, mammalian species contains some non-infective agent which, on parenteral injection, produces disease in the nervous system. The slow growth of our knowledge of this phenomenon over the past sixty years, from the era of study on the neuroparalytic accidents of anti-rabic treatment, to the modern era following the development of the Freund adjuvant technique to produce the lesions quickly and regularly, is a story now well known.

### *General Features of the Method*

In résumé, this strictly neurological disease is produced regularly by a single, or a few, parenteral injections of sterile homologous or heterologous brain tissue emulsified in a viscous base of paraffin oil and lanolin fortified by heat-killed tubercle bacilli. In the case of monkeys in whom a cerebral lobectomy can be performed more readily than in the more lowly laboratory creatures, the animals' own brain tissue has been shown to be effective when injected intramuscularly with adjuvants (Kabat *et al.*, 1949). Adjuvants alone, or adjuvants plus liver, lung, kidney, skeletal muscle, adrenal gland, testis, placenta and skin (Lumsden, 1949) have failed to produce encephalitis or even comparable disease in other organs. Thus, in a consecutive series of twelve experiments where adjuvants and whole

[1]*Present Address*: Maida Vale Hospital for Nervous Diseases, London, W.9.

brain tissue were given to guinea-pigs (as "positive control experiments" in connexion with other work on this problem) I have found the histological changes of the disease each time, with an incidence from 75% to 100% in each series; in all, in 238 out of 297 animals. On the other hand, in a series of 197 animals injected with adjuvants plus tissues other than brain or nerve, there were no histological signs of the disease in any animal. Transmissibility tests with brain tissue, serum, and cell exudates and suspensions have been negative (Kabat *et al.*, 1948).

*Distribution in Species*

This experimental disease has been most extensively studied in the monkey, guinea-pig and mouse, but it is readily produced also in the rabbit, dog, sheep, and goat (in last, own unpublished observations). The only mammalian species strikingly resistant so far found is the rat—an animal notoriously difficult to sensitize. But even with the rat, using over 150 animals, since an earlier negative report (1949), I have been able now to produce the typical lesions in two rats. The active substance in the brain has been shown by various authors to be present in the monkey, guinea-pig, mouse, rabbit, dog, sheep, goat, ox, human, and even in the chicken brain but it is apparently absent from frog and fish brain (Kabat *et al.*, 1948) though not extensively tested in these.

Though the incidence of the disease, and the number of visible lesions caused, may vary with the species, and can be modified to some extent with the dosage of the active constituents of the emulsion used, yet in my experience the disease is remarkably constant in its histological picture throughout all species, and remarkably characteristic.

*The Role of the Adjuvants*

Earlier work (Rivers and Schwentker, 1935; Ferraro and Jervis, 1940) showed beyond all doubt that brain tissue alone without adjuvants can produce the disease. The role of the adjuvants is purely potentiating and experiment has indicated that for this effect they must be given at the same site as the brain, though more work is called for on this. The adjuvants increase the result so that in monkeys, guinea-pigs and mice an almost 100% result can be predicted. It is this enhancing effect which is, of course, the most powerful argument in favour of an immunity or sensitization mechanism, since their use arose from their enhancing effects experimentally on simpler systems such as sensitization to horse serum, egg white and tuberculin, in immunization with diphtheria toxoid and *Bact. typhosum*, and they had already been found to raise the titres of complement-fixing antibodies tested *in vitro* with extracts of brain tissue on the sera of animals injected with brain. Of these adjuvants, the paraffin and the wool-fat base—a mixture of oxycholesterol and several cholesterols—certainly play an indirect role, partly mechanical in keeping the brain tissue longer in situ, and partly evocative of a pronounced local reticulo-endothelial response. But these can be omitted without great loss of effect. Experimentally, the important adjuvant is the heat-killed tubercle bacilli—BCG is also effective—but in place of these other mycobacteria like *M. butyricum*, *M. phlei*, and *Nocardia asteroides* have been effective; and even non-acid, non-alcohol-fast variants of butyricum which can be produced by growing on glycerin-poor media (Freund, Lipton and Morrison, 1950). In a collateral field of research a good deal of work is at present being done on the biologically active fractions of the bacillus in the production of the characteristic cell changes in the tuberculous follicle. In that field, lipids, fatty acids and polysaccharides have been mainly incriminated. However, in the adjuvant action in "allergic" encephalomyelitis the recent findings of Colover (1954) point to the agency of a somatic protein constituent of the bacillus rather than a lipid or wax.

*The Factor in the Injected Brain Tissue*

The responsible factor in the injected brain tissue is highly resistant to physical treatments like heat, drying *in vacuo*, ultrasound, and to prolonged conservation. Thus it was still present in one batch of emulsion after three years' storage. Prolonged autoclaving showed no alteration, and prior fixation of the brain tissue for some days in formalin before making the emulsion showed only some slight loss of potency, and perhaps not significant. Incidentally, all of this sort of work, one sees from reports, tends to be carried out on inadequate scale for reasons of financial economy, and discrepancies in results are probably most frequently due to this cause. Prolonged alcohol and acetone extraction, removing most of the soluble lipids, did not affect its potency (Lumsden, 1949), indicating that the active agent was protein or protein-bound, rather than a soluble lipid. As for its distribution in the nervous system Kabat (Kabat *et al.*, 1948) found it to be absent from young unmyelinated rabbit fœtal brain but present in three-day rabbit cord and absent in twelve-day rabbit cerebrum—in this respect apparently running parallel to myelinogenesis.

One puzzling feature of the evidence otherwise incriminating a myelin factor was the finding that adult peripheral nerve was apparently not encephalitogenic in some species

Thus, in their original work, Kabat and his co-workers (1947) and Morgan (1947), independently, had both obtained negative results in monkeys injected with monkey peripheral nerve. However, in guinea-pigs injected with guinea-pig peripheral nerve I obtained the typical encephalomyelitis in 5 out of 12 animals tested (Lumsden, 1949). This has stood for some time as an isolated finding but has now been confirmed this year by Waksman and Adams (1955).

But now with the paper of Waksman and Adams a momentous advance has been made. Whereas earlier workers had reported negative findings on histological examination of the monkeys and guinea-pigs injected with homologous brain and peripheral nerves, Waksman and Adams have now discovered, in rabbits, that when rabbit sciatic nerve or spinal ganglia are injected intradermally, lesions develop only in the peripheral nerves, roots and ganglia; and furthermore, that these changes are associated with a marked increase of protein in the cerebrospinal fluid without pleocytosis—a "dissociation albuminocytologique" which, as the authors point out, exactly mimics the picture in the Guillain-Barré syndrome and Landry's paralysis. Thus, two new and exciting aspects of the problem are at present unfolding, namely (1) an extension of the problem, as it is related by inference to human disease, to embrace a group of diseases of the peripheral nervous system of hitherto unexplained ætiology, and (2) an extension of the biochemical problem on the relationships, and differences, in the agents in peripheral and in central nervous tissue—for there are evidently different antigenic factors.

The chemical stability of the factor and the ready biological test for its presence in the form of the experimental disease afford good reason for the hope that it can be isolated and identified before long. This would now seem to be the master key to the problem since, as will be seen presently, immunological research in this field has got bogged down because of the lack of a reasonably pure antigen. Some progress has already been made since the earlier tests on crude sphingomyelin, cerebroside, lecithin and cephalin fractions which were tried at first. Olitsky and Tal (1951, 1952) have now tried a group of substances recently discovered by Folch and Lees (1951), and called by them "proteolipids". These are lipoproteins which are soluble in chloroform-methanol-water mixtures but, unlike previously-known lipoproteins, insoluble in water and therefore more lipid than protein—hence the special designation. Neither of the proteolipids so far isolated is pure, but together

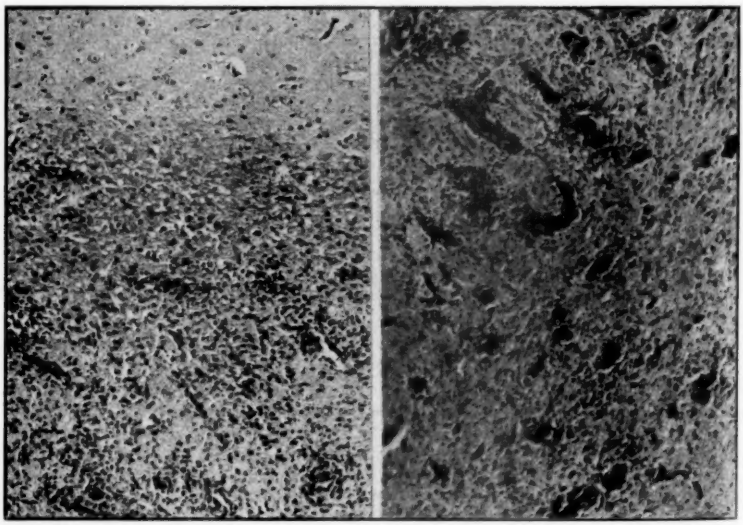

FIG. 1. FIG. 2.

FIG. 1.—Guinea-pig brain. Shows the intense vascular and histiocytic reactions which involved the *whole* white matter, as here, but spared the cortex—portion of which is included in the upper quarter of the picture.

FIG. 2.—Guinea-pig brain. White matter. Showing the severity and character of the cell proliferation within the vessel walls.

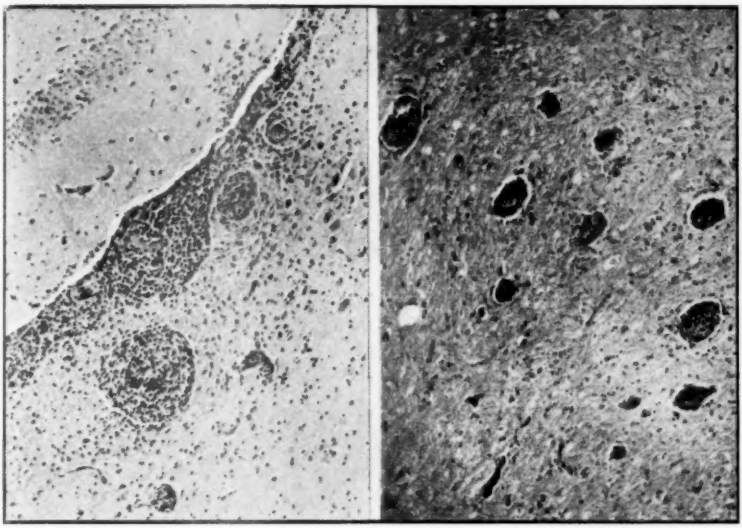

Fig. 3. Fig. 4.

FIG. 3.—Guinea-pig brain. In top left corner is seen part of *cornu Ammonis*. Note the exuberance of the mesenchymal reaction in walls of a large terminal vein and tributaries; little histiocytic reaction in parenchyma.

FIG. 4.—Guinea-pig brain. The reaction consists of a mesenchymal proliferation in the venular walls. There is no "perivascular reaction"; and only in 1 out of 7 veins involved is there associated histiocytic (microglial) increase within the parenchyma. An arteriole (bottom, extreme right) shows no cellular reaction.

Proteolipids A and B, which contain only about 5% of the total solids of the white matter, contain practically all the encephalitogenic activity present in the brain.

*Analysis of the Inflammatory Reaction in the Brain*

The experimental lesions in the brain are microscopically highly characteristic, consisting of a cellular increase in the walls of the veins and venules, with a variable and less constant degree of microglial proliferation within the surrounding parenchyma associated with damage to the myelinated fibres. All authors agree about this and all find in this the essential visual similarity between these experimental lesions and the post-infectious myelinoclases in man. But in my view, the nature and significance of the vascular changes particularly have not been fully appreciated, and it is with these I should like mainly to deal. My subsequent remarks are based on recent studies on the cytology of the process; and a detailed account of this, along with a discussion of the reason for the special involvement of the venular system, is under preparation for publication elsewhere.

In all species, the white matter is chiefly affected, the grey less so. Some cellular infiltration of lymphocytic type is not uncommon in the surface meninges but this has been overemphasized, and "encephalomyelitis" is still the best description. In the course of examining the brains of over 1,000 guinea-pigs in these experiments over the past eight years I have been struck with the frequency of those cases in which there are severe confluent lesions involving the whole of the white matter of the cerebrum and completely sparing the grey (Fig. 1). Fig. 2 illustrates the severity of the reaction in these confluent lesions of the white matter. There is a cellular reaction in the walls of the vessels, spilling over, as it were, into the parenchyma to merge with the glial reaction in a curious and characteristic manner. This is neither "perivascular cuffing", nor is it "granuloma formation" in the commonly used senses in histology, but a highly typical reaction. The severest reactions—and, in the mildest cases occasionally the only visible lesions—are located in the subependymal white matter throughout the whole ventricular system, and here the terminal veins are conspicuously concerned. Often, even in this "site of election" for lesions (Fig. 3) the microglial reaction is minimal or absent, and the cellular reaction in the vein wall is sharply limited; Fig. 3 shows what is perhaps the most representative histological picture of the process—the curiously exuberant reaction within the vein wall.

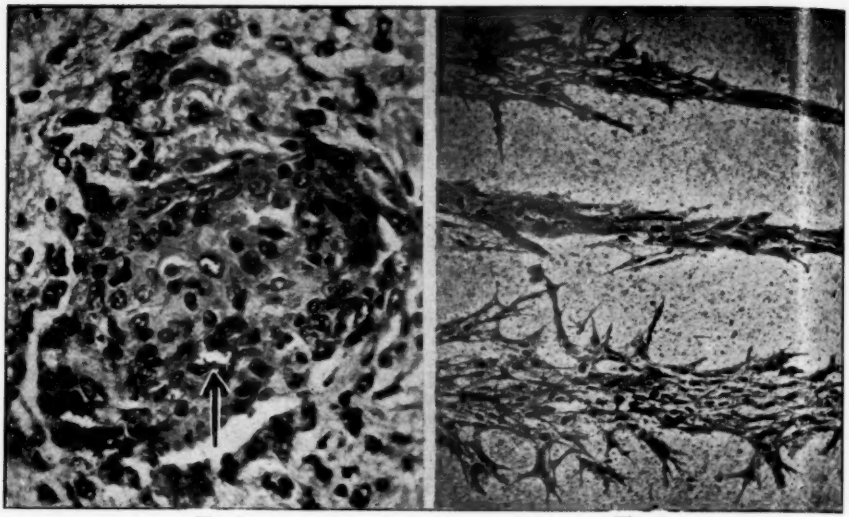

Fig. 5. Fig. 6.

FIG. 5.—Guinea-pig brain. High-power view of a venule (red cells and lumen indicated by arrow) showing the profuse proliferation of mesenchymal cells with poorly defined cell outlines (the "mesenchymal *continuum*" referred to in text).

FIG. 6.—Mesenchymal, or "mesothelial", cell outgrowth in tissue culture from a fragment of white matter of guinea-pig brain in a case of "allergic" encephalomyelitis. Differs quantitatively only from mesothelium grown from normal adult brain explants (*see* text).

The microglial reaction is thus not an essential element of the lesions, nor, likewise, is the evidence of damage to the parenchyma, revealed when it is present as an ill-defined sleeve of demyelination. But in my experience these do not remain selectively demyelinating in the way plaques of multiple sclerosis do, and they progress to ill-demarcated glial scars, usually with evidence of gross tissue destruction. The question of quantitative differences in various species will be discussed in a report elsewhere; but the subsequent comments are applicable to the material from the monkey, goat, and rat, as well as the guinea-pig, which has been personally studied.

In a typical case (Fig. 4) most of the vein walls show their cellular reaction though a few escape for no apparent structural reason even in the same region. This illustration (Fig. 4) shows how intense this reaction is, and that it is an integral part of the vessel wall, not an infiltrate of cells within the perivascular spaces such as is commonly seen in chronic microbic and virus encephalitis. The detail seen under high power (Fig. 5) in a typical instance shows the great increase in width of the wall with complete loss of distinction between the endothelium and the adventitial or reticular elements. Even cell outline is lost so that, as seen here, the pale vesicular nuclei appear free in a syncytium of cytoplasm, or *continuum*, incidentally recalling cogently Babes's and Mironesco's description originally (1908), of the "wide embryonic zone" of cells in the lesions of the post-paralytic accidents of anti-rabic treatment. This cell response in the wall of the vessel is, in my experience, the usual visible expression of the process at work in the brain in this disease and it is this which has been variously described as a "perivascular infiltration" of "epithelioid-like histiocytes", "epithelioid mononuclears", "monocytes", "leucocytes", "lymphocytes", "granulomatous reaction", "plasma cell", "plasmacytic reticulum cell", and "reticulo-endothelial", &c., and which, in a *quantitative sense* is certainly characteristic of the disease process. Furthermore this is often the only visible change in the mildest cases, or, as in an experiment specially carried out to investigate this question, in animals killed off in batches every few days before the usual period for the onset of symptoms.

The method of tissue culture gives a clearer understanding of the nature of these cells than histological study and now affords the interesting possibility of visually testing cells for sensitivity in a way which space does not permit to describe here but which was used by Rich and Lewis (1932) to test the sensitivity of macrophages from guinea-pigs sensitized to tuberculin. Vascular connective tissue cells from normal brain explants, and from tumours, which we have studied, are of three distinct types: First, an endothelial-

like cell which characteristically grows in sheets and broad columns, with very frequent mitosis, and is occasionally seen to undergo transition to fibroblasts and macrophages. The second and third types are differentiated fibroblasts and macrophages which also undergo mitosis but seem to breed true at this stage. These observations are in accord with Maximov's classical observations on tissue culture. It will be recalled that Maximov regarded the pluripotent endothelial-like cell as a primitive mesenchyme cell which he said persists as such in the mesodermal vascular fabric of the adult organism. In cultures of adult brain, where other mesodermal stroma is lacking, it is often easy to trace the migration of these mesenchymal cells from the adventitial aspect of the vessels, not from the endothelium. Now, in a series of carefully controlled experiments (to be reported elsewhere in detail) it has been found that fragments of white matter from the experimental "allergic" encephalomyelitis consistently show a much richer outgrowth of macrophages, fibroblasts and especially of the endothelial-like mesenchymal cells. In the case of this last cellular component, there is great mitotic activity. But, while the outgrowth of all of these types of cell is accelerated, their individual cytological characteristics are not abnormal. In cultures, these mesenchymal cells show a striking, and highly characteristic, cytoplasmic fusion (Fig. 6) which suggests an explanation for the curious syncytial-like feature of the cellular reaction in the vein wall in the histological material (Fig. 5). Thus, living cytological studies seem to indicate clearly that the essential reaction in "allergic" encephalomyelitis is a proliferation of the perivascular mesenchyme rather than of differentiated plasma cells or other of the more classical "inflammatory" types of cell (neutrophils, eosinophils, lymphocytes).

Whatever the origin of the plasma cell, in culture it has not been seen to revert into a "mesenchyme cell" nor have the latter been found to change into plasma cells.

The excessive growth of the mesenchymal element in cultures from "allergic" encephalitic material seems to indicate that this cell is in some way *pre-stimulated* in the process, and it is therefore at this level that we should look for evidence of the antigen-antibody reaction if such is involved in this disease. From recent studies on the pharmacological mechanisms underlying inflammatory reactions generally, evidence has been accumulating to indicate that these mesenchymal elements in vessel walls are the main factories of hyaluronidase. It may therefore be that this or some other similar spreading factor, like a protease, *may be the agent responsible for the parenchymal damage when it occurs*, and that it is the excessive stimulation of this mesenchyme of the brain which results in the liberation of deleterious amounts of these secondary spreading substances, with resulting "myelinoclasis". Stating it another way, the whole process may be looked upon as an overloading of the blood-brain-barrier and its eventual breakdown, with the liberation, secondarily, of myelinoclastic factors from the hyperplastic mesenchyme. Thus, the experimental "allergic" encephalitis may be of further use as a tool with which to explore problems of the blood-brain-barrier.

*Immunological Considerations*

Even prior to the adjuvant era there had accumulated a considerable dossier of facts on the specific antigenicity of brain and brain fractions *in vitro* (Witebsky and Steinfeld, 1928). In animals injected with brain and the adjuvants a complex pattern of antibody response has been found in the three investigations so far carried out (Lumsden *et al.*, 1950; Thomas *et al.*, 1950; Waksman and Adams, 1955) but no one has yet been able to demonstrate any clear parallel between the experimental disease and these soluble antibodies *in vitro*. The difficulty lies, of course, mainly in the complex mixtures of potentially antigenic substances contained in the emulsion necessary to produce the disease. That the injection of homologous material also provokes the formation of non-soluble cell-fixed antibodies is also evident from the tuberculin-type sensitivity to homologous nervous tissue which develops and here a closer parallelism in time and degree with the disease is exhibited (Waksman and Adams, 1955). But again this latter type of approach has so far afforded no clear insight into the pathogenesis of the process.

Efforts at immunization, desensitization, and prophylaxis by salicylates, antihistaminics and ACTH, which have all had some apparent partial success help to support the idea that hypersensitization may be involved in the genesis of the encephalitis but I do not think that any of the results have been clear-cut or technically satisfactory.

## Conclusion

In conclusion, we may reduce the problem to its simplest by saying that here we have a biochemical mechanism capable of producing severe disease of the nervous system central and peripheral, and that it is of a microscopically visible inflammatory type. It usually far exceeds the most severe infective processes in its structural manifestations and any cognate experimental lesions in other organs which have been produced with antisera, drug hypersensitization and so on. In this respect it can truthfully be said that the process opens up a field of structural pathology as revolutionary as the discovery of the bacteria.

If hypersensitization, or allergy, is in fact involved, then neuro-allergy becomes a scientific fact of the utmost respectability and no longer a somewhat disreputable hypothesis concocted to cloak ignorance. Furthermore, the experiment with the animal's own brain shows that *auto*-sensitization is a real possibility. It is in this field that some of us are beginning to feel that we must search for the causative mechanism, not only of the post-infectious myelinoclases, but of multiple sclerosis also. But at the moment we have no clues to the missing links in the chain of the causative processes. How can the experimental process be duplicated in human disease? Is some type of antigen, specific for myelinated nerve fibres, formed by conjugation of a haptenic proteolipid from the patient's own nervous system with the appropriate type of protein derived from a source exogenous to the brain? Experimentally, we have seen that the brain and adjuvant have had to be given at the same site. But we must remember that the original observations on adjuvant action were made with unaccompanied antigens injected into tuberculous animals, i.e. with an "adjuvant" depot already in the tissues elsewhere. Could this mechanism apply, not with the 100% efficiency of the experimental set-up, but sporadically in human disease? In this respect the association of tuberculosis and Schilder's disease which has been commented upon more than once by experienced neurologists, might be significant. Experimentally, too, the antigen has had to be given parenterally; but there remains untested the disturbing possibility that even oral intake might suffice in some individuals. Thus, quite apart from "auto-sensitization" and the question of the relationship of this mechanism to the human post-infectious encephalitis, perhaps the somewhat bizarre conditions of the experimental disease may be fulfilled in the case of human beings more literally than we have so far dared to imagine.

## REFERENCES


BABES, V., and MIRONESCO, T. (1908) *C.R. Soc. Biol., Paris*, **64,** 964.
COLOVER, J. (1954) *Brain*, **77,** 435.
FERRARO, A., and JERVIS, G. A. (1940) *Arch. Neurol. Psychiat., Chicago*, **43,** 195.
FOLCH, J., and LEES, M. (1951) *J. biol. Chem.*, **191,** 807.
FREUND, J., LIPTON, M. M., and MORRISON, L. R. (1950) *Arch. Path.*, **50,** 108.
KABAT, E. A., WOLF, A., and BEZER, A. E. (1947) *J. exp. Med.*, **85,** 117.
——, ——, —— (1948) *J. exp. Med.*, **88,** 417.
——, ——, —— (1949) *J. exp. Med.*, **89,** 395.
LUMSDEN, C. E. (1949) *Brain*, **72,** 198, 517.
——, KABAT, E. A., WOLF, A., and BEZER, A. E. (1950) *J. exp. Med.*, **92,** 253.
MORGAN, I. M. (1947) *J. exp. Med.*, **85,** 131.
OLITSKY, P. K., and TAL, C. (1951) *Proc. Soc. exp. Biol., N.Y.*, **78,** 607.
——, —— (1952) *Proc. Soc. exp. Biol., N.Y.*, **81,** 590.
RICH, A. R., and LEWIS, M. R. (1932) *Bull. Johns Hopk. Hosp.*, **50,** 115.
RIVERS, T. M., and SCHWENTKER, F. F. (1935) *J. exp. Med.*, **61,** 689.
THOMAS, L., PATERSON, P. Y., and SMETHWICK, B. (1950) *J. exp. Med.*, **92,** 133.
WAKSMAN, B., and ADAMS, R. (1955) *J. exp. Med.*, **102,** 213.
WITEBSKY, E., and STEINFELD, J. (1928) *Z. ImmunForsch.*, **58,** 271.


**Dr. J. Colover** drew attention to recent work on the subject of experimental allergic encephalomyelitis which had been done in collaboration with Dr. R. Consden at the Canadian Red Cross Memorial Hospital, Taplow, England (Colover, 1954; Colover and Consden, 1955; Colover and Consden, 1956).

Commencing with the residue left after extracting heat-killed human tubercle bacilli with acetone and isopropyl ether and subjecting this residue to successive treatment with alkali, acid, proteolytic enzymes, and extraction with *n*-butanol, benzene and a mixture of chloroform and methanol ($\frac{2}{1}$ V/V), it had been possible to obtain a residue which was less than 25% by weight of the whole tubercle bacilli. After incorporation in an emulsion (0·5 mg./ml.) containing Falba, Bayol F and homologous brain suspension, this material was injected intramuscularly into guinea-pigs and it produced the clinical and histological features of experimental allergic encephalomyelitis in more than 50% of them.

Analysis of this active residue showed that it had a high protein content, about 70%, mycolic acid 9·8%, and some polysaccharide. The mycolic acid had been identified after its recovery from the hydrolysed residue by its melting point and the lack of depression of the melting point when mixed with an authentic sample of mycolic acid. The protein, on hydrolysis, yielded mostly glutamic acid, alanine and some diaminopimelic acid. Various lipid, protein and polysaccharide extracts obtained from the starting material did not have activity. Samples of methyl mycolate and the lipopolysaccharide wax D (Asselineau, 1952) which had been supplied by Dr. E. Lederer of Paris, were also found to be inactive when used at the same strength as the active residues. It therefore seems possible that the active agent in the tubercle bacillus is an insoluble compound which is mainly formed from the above amino acids together with the long-chain fatty acid, mycolic acid.

## REFERENCES


ASSELINEAU, J. (1952) *Bibl. tuberc.*, **6,** 1.
COLOVER, J. (1954) *Brain*, **77,** 435.
——, and CONSDEN, R. (1955) *Excerpta med., Amst.*, VIII, **8,** 808.
——, —— (1956) In press.

Dr. **William Gunn** pointed out that severity was associated in a general way with the nature of the primary disease although for each specific fever the incidence and severity appeared unrelated to initial severity. Vaccination was a recognized notable exception to the general rule, and he was surprised to learn of a 50% mortality in the rubella series. The clinical manifestations of the last-named disease were extremely variable, as Australian experience in connexion with congenital defects amply showed, and diagnosis in sporadic cases may only be possible by virus culture and complement-fixation techniques.

He favoured the specific virus hypothesis as to ætiology because (*a*) virus has been recovered from the brain of fatal measles and vaccinia cases and is probably present at the outset in all cases; experience of human and simian poliomyelitis has shown that virus dies relatively early in nerve tissue on account of the rapid local production of neutralizing substances; (*b*) although onset is usually in the convalescent stage of the primary disease it may occur earlier, even before, and in the case of mumps at least, occasionally in the absence of subsequent clinical attack—in which case the diagnosis may be based upon the rising titre of blood complement fixing bodies; (*c*) spinal fluid changes, usually associated with milder forms, in the case of mumps include presence of the virus. Normal fluids are admittedly not uncommon in severe encephalitis, notably epidemic encephalitis and poliomyelitis, both recognized as virus diseases.

Treatment is unsatisfactory for reasons equally applicable to poliomyelitis and other neurotropic diseases, largely because the main damage is usually inflicted at the outset and specific antiserum is therefore too late to be of value. On the other hand, as cerebral œdema is a marked feature of severe cases, characterized by vomiting, stupor or extensive paralyses, intravenous administration of concentrated (three to four times) plasma is a rational, and may prove a life-saving, procedure; Dextran is potentially dangerous in concentrated solution while sodium sulphate and glucose in the usual strengths are excreted or metabolized too rapidly to exert a demonstrable therapeutic effect. Continuous infusion of 40% glucose into the vena cava by catheter might prove effective as has been demonstrated in some forms of renal failure. The results of cortisone therapy so far recorded can be regarded as no more than suggestive; antibiotics and oxygen tent therapy have improved the prognosis significantly, making comparison of current fatality rates with those of earlier series largely invalid.

**Dr. W. F. Twining McMath** stated that during the period spring 1951 to spring 1953, 10 cases of measles meningo-encephalomyelitis came under his care at Neasden Hospital. Of these, 3 occurred in the pre-eruptive stage on the first, first and fourth days respectively of illness, and three, three and two days respectively before the appearance of the rash. The spinal fluid changes, pleocytosis and increased protein were present, the pre-eruptive cases showing no difference from the post-eruptive cases.

The sole fatality occurred five days after admission to hospital, in a fulminating pre-eruptive case appearing two days before the rash. ACTH was given in this case for thirty-six hours immediately preceding death, and in another case which recovered, for eight days, without any apparent influence upon the course of the disease. In 4 of the 10 patients, coma lasted for two, five, fourteen, and fourteen days respectively. The coma and severe paralysis are bad prognostic signs, but no case is necessarily irreversible, and complete recovery may occur; the most likely sequelæ being behaviour problems.

It was perhaps significant to remark that in view of the suggestion that this complication has an allergic basis, in no case was eosinophilia encountered.

**Dr. L. J. M. Laurent** said that the allergic theory of post-infectious demyelinating encephalomyelitis was now based on a good deal of experimental evidence. He thought that the clinical features, too, tended to support the allergic theory. The complication bore no relation to the severity of the original virus infection, it occurred commonly between the seventh and the twelfth day of the disease, at a time when antibodies were being formed and it tended to a spontaneous and complete recovery in a few days to two months, even in apparently hopeless cases. As regards the day of disease, it was important to bear in mind that the day of the rash was not the first day as the patient was often infectious for a few days before. The case mortality given in Dr. Miller's series seemed much too high. In ten years at one infectious diseases hospital there had been 17 cases of post-infectious encephalomyelitis: 11 cases after measles, 3 after chickenpox, 2 after rubella, 1 after mumps with only one death, after measles. Some of the recovered cases had been very mild, but there had been also 4 very severe ones. It is possible that the milder cases were not always recognized or recorded.

If he understood the allergic theory correctly, a reaction between an antigen derived from the virus and its antibody set free some toxic substance which diffused into the nervous tissue round the vessels and damaged the myelin. This toxic-allergic conception was not new in medicine, it had been for many years the explanation of rheumatic fever and glomerulo-nephritis after streptococcal infections. In one case there was damage to the collagen of connective tissue and in the other damage to the myelin of nervous tissue. There was an obvious parallel which it was not safe, however, to carry too far.

On the question of treatment, skilful and devoted nursing took first place, the repeated injections of hypertonic (50%) glucose seemed to produce improvement in a few cases. He had not tried cortisone or ACTH and would be glad to know the experience of those who had. Convalescent measles serum had been advocated for some years for post-measles encephalitis. He had given

it in one case of moderate severity who became worse and died six hours later. Similar instances of the patient's deterioration after convalescent serum had been reported in recent French medical literature.

Of the neurological complications of whooping cough, convulsions were the outstanding feature. Some convulsions were obviously the result of anoxia following on apnœic attacks, lung collapse, or bronchopneumonia; they were short and if the anoxia could be corrected they did not recur. Other convulsions were due to an intercurrent meningitis, tuberculous, pneumococcal or influenzal; a lumbar puncture settled the diagnosis and indicated the treatment. There was a third type of convulsions, however, which was peculiar to whooping cough and which had been called "whooping cough eclampsia". These convulsions occurred in the third or fourth week only and independently of all anoxia, the patient passed into *status epilepticus* and 95% of the cases ended fatally in one to three days. The C.S.F. was under pressure but, in his experience, was always normal. Post-mortem examination showed an œdematous mauve-coloured brain, there was no vascular lesion, no demyelination and no evidence of perivascular cuffing. It had been termed a "toxic encephalopathy", but it was not clear which toxin was meant. The well-known toxin of *Hæmophilus pertussis*, isolated by Evans and Maitland, was not a cause of illness in whooping cough patients and their recovery was not associated with the production of antitoxin. There was need of more accurate research in the nervous complications of whooping cough.

**Dr. J. C. McEntee** said that in thirty years' experience of the acute infectious diseases he had only once seen encephalomyelitis complicate scarlet fever and had never seen so-called benign aseptic meningitis in the early days of scarlet fever.

He also said that recently a colleague in another hospital had treated with cortisone two children who had measles encephalitis. Both children had died, an event which suggested that the treatment had an adverse effect. Death from measles encephalitis or encephalomyelitis was, in his experience, uncommon.

## BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

**Cope (Sir V. Zachary).** A hundred years of nursing at St. Mary's Hospital, Paddington. pp. 144. London: Heinemann. 10s. 6d. 1955.

**Critchley (Macdonald),** ed. James Parkinson (1755–1824): a bicentenary volume of papers dealing with Parkinson's disease, incorporating the original "Essay on the Shaking Palsy". pp. 268. London: Macmillan. 15s. 0d. 1955.

**International Anatomical Nomenclature Committee.** Nomina anatomica, revised by the International Committee appointed by the 5th International Congress of Anatomists, . . . Oxford, . . . 1950. pp. 83. London: privately printed. 1955.

**Magonet (A. P.).** Hypnosis in asthma. pp. 95. London: Heinemann. 7s. 6d. 1955.

**Moriyama (H.).** Immunity. pp. 203. Tokyo: Shonan Hygiene Institute. $5.00. 1955.

**Moriyama (H.).** The nature of viruses and the origin of life. pp. 454. Tokyo: Shonan Hygiene Institute. $7.00. 1955.

**North Atlantic Treaty Organisation.** Advisory Group for Aeronautical Research and Development. Collected papers on aviation medicine. pp. 209. London: Butterworth. 1955.

**Sharpe (W.).** Humanity and the man: a poem. pp. 130. Dublin: Hodges, Figgis. 1881.

**Thomson (Sir StClair).** Diseases of the nose and throat. Revised by V. E. Negus with the assistance of G. H. Bateman. 6th edit. pp. 1040. London: Cassell. 90s. 0d. 1955.

**Toldt (C.).** Anatomischer Atlas. 6te Aufl. pp. 974, 6 parts. Berlin and Vienna. 1908.

**War Office.** Manual of army health 1954. pp. 686. (London: War Office.) 1955.

# Section of Anæsthetics

President—T. Cecil Gray, M.D., F.F.A.R.C.S., D.A.

[*September* 30, 1955]

## Pædiatric Anæsthesia [*Abridged*]

By M. Digby Leigh, M.D., F.F.A.R.C.S.

*Children's Hospital, Los Angeles*

The surgical correction of congenital deformities has presented anæsthetists with a new and challenging field of endeavour because these operations are occurring at an earlier and earlier age. For example, our statistics for the period June 1954 to June 1955 show that out of a total of 5,239 cases, 574 were operations on infants under 1 year of age.

Most infants who die on the operating table die from hypoxia of primary respiratory or circulatory origin.

*Pulmonary physiology and anatomy of the newborn.*—First a normal day-old infant has been reported by one observer to have a respiratory rate from 27 to 82 per minute, a tidal air from 10–27 c.c., and a minute volume from 225–1,187 c.c. We recognize immediately the tremendous span of these figures. I would like to draw particular attention to the tidal air. The normal tidal air can be reduced very easily by sedative drugs or some of the anæsthetic agents. On the other hand, a crying newborn has a tidal air of approximately 160 c.c., and it is a known fact that an infant can cry for long periods of time. Later on, it will be shown how this tremendous range of tidal air is utilized during the conduct of anæsthesia in order to maintain an adequate pulmonary ventilation and, in most cases, an adequate oxygenation.

The next point to note is the commonly occurring periodicity of respiration, especially in the premature or in the infant depressed with premedication. This periodicity can be so marked in some instances that it hinders oxygenation and the anæsthetization with inhalation agents.

The third important point is, that the infant for its weight has a very high oxygen consumption, and, at the same time, has a very high carbon dioxide production. We are thinking in terms of at least double the oxygen requirement per kg. of body weight compared with that of the adult.

The fourth point to recognize is that, anatomically, the newborn normally has a relatively large trachea and bronchi, incomplete alveolation, and an abundant pulmonary mesenchyme. Perhaps some of the blood coursing through the lungs is never exposed to the diffusing alveolar oxygen.

We may then theorize that severe hypoxia occurring rapidly in the infant is due to the high oxygen requirement, the relatively large trachea and bronchi, and finally the incomplete alveolation, and, at times, residual areas of atelectasis.

There are, in addition, many natural and artificially produced respiratory abnormalities which threaten oxygenation.

Generally, the infant is a nose breather, but should large adenoids or a posterior choanal atresia block the nasal air passage, often the firm little tongue will act like a valve against the palate producing a total respiratory obstruction. In some cases, such as laryngomalacia, the cartilages of the epiglottis and arytenoids are somewhat soft and immature, and are readily sucked into the glottis on inspiration.

Then again, one cannot overlook the possibility of laryngospasm occurring, for the newborn seems to contract this more readily than the adult. Local anæsthetic sprays, deep anæsthesia and muscle relaxants, however, have proved helpful in preventing laryngospasm.

Furthermore, the trachea and bronchi of the newborn have poorly developed cartilage and at times the trachea itself may become kinked and obstructed. In the flexed infant, both bronchi may become totally occluded as they course over the pulmonary blood vessels.

The newborn often demonstrates abnormal aggravating changes in the pulmonary tissue. In the premature, a hyaline membrane lining the alveoli is one example. Then again, on occasion, the anæsthetist faces a three- or four-hour tracheo-œsophageal fistula operation in an infant which already has some atelectasis and pneumonia.

It is possible to enumerate many conditions which interfere with the full expansion of the lung tissue, such as pneumothorax, cysts of the lungs, agenesis of the lung, diaphragmatic hernia, diaphragmatic paralysis, and that comparatively common impediment—distension of the stomach.

In most instances, the signs of acute hypoxia are the same, regardless of origin Deepening cyanosis and later pallor are still useful indications, but continuous monitoring of heart

sounds through a præcordial stethoscope is one of the most reliable methods of detecting hypoxia. The thin chest wall of the newborn makes the heart sounds readily audible. The infant's heart responds quickly to the acute lack of oxygen by a marked slowing of the rate and diminishing force of contraction. This generally can be elicited through the præcordial stethoscope with a single plastic earpiece which supplies the anæsthetist with a continuous record of the rate and tone of the heart.

To recapitulate, extreme bradycardia and diminishing audibility of heart sounds are diagnostic of severe hypoxia.

In some instances, evidence of hypoxia can be obtained by the continuous ECG record illuminated on the cathode-ray oscilloscope.

In many of our very small infants both præcordial audition and ECG recordings are used, but it must be remembered that the mere presence of an ECG complex does not indicate that the heart is circulating the blood efficiently. Hypoxia in the infant usually demonstrates in the ECG record a bradycardia, low take-off of the S–T segment, and a widening of the Q.R.S. complex.

Seldom would any of these signs of acute hypoxia occur if the lungs were adequately ventilated with oxygen at all times. This is accomplished by ensuring:

(1) Adequate oxygen in the inspired air.
(2) Patent airway.
(3) Adequate tidal air and minute volume of respiration.

*Adequate Oxygen in the Inspired Air*

In the first place, the light stages of open drop ether have stood the test of time because respiration is stimulated. Consequently, if one does not blanket the open drop ether mask with numerous towels and exclude the oxygen of the atmosphere, the patient will be adequately oxygenated. The common error is to use too many drapes around the mask in order to take advantage of the increased stimulation of respiration by rebreathing exhaled carbon dioxide. Under these circumstances, there may be inadequate oxygen in the inspired air. A fatality seldom occurs under these circumstances since the anæsthetist notices the cyanosis, lifts off the mask, and allows the patient a breath of air. Nevertheless, in the very ill patient oxygen-lack for a few moments can dilate the heart and cause a marked degree of circulatory depression. In these cases, it is recommended that one litre per minute of oxygen be flowed under the mask to supply adequate oxygen and remove some of the exhaled carbon dioxide. Open drop ether is still employed by a large number of anæsthetists who do not use the improved adult methods of modern anæsthesia in the infant and young child. I am convinced that this same group of anæsthetists would seldom select open drop ether in an adult for major surgery.

In the last few years, manufacturers have developed smaller pieces of anæsthetic apparatus so that now it is possible to do "no rebreathing", "partial rebreathing", "to-and-fro absorption" or "absorption in circuit". These methods provide greater control of the anæsthetic and oxygen mixtures.

*Patent Airway*

Ensuring adequate oxygen in the inspired air serves no purpose if the airway is obstructed. Tongue, tonsils or adenoids may cause an upper respiratory obstruction. If manipulation of the lower jaw fails to relieve this obstruction, a pharyngeal airway is inserted. If obstruction occurs lower down in the air passages, say, in the larynx, a free airway can be guaranteed only with an endotracheal tube. Seldom, however, is a cuff necessary. Preference is given to a thin, firm-walled, plastic tube of the proper size for the case at hand. Care must be exercised to avoid an endobronchial intubation. Even a properly placed endotracheal tube does not ensure patency of the bronchi. An acutely flexed infant may show kinking of his soft-walled bronchi, and it is advisable to extend the infant by means of a pad placed under the middle of the back.

An endotracheal tube also prevents stomach contents from entering the trachea. In spite of the presence of a stomach tube, pressure on the stomach by the surgeon during intra-abdominal operations may push the gastric contents up the œsophagus around the stomach tube and into the pharynx, where it could be aspirated into the trachea if the patient were not intubated.

*Adequate Tidal Air and Minute Volume of Respiration*

The ordinary tidal air in the newborn of 23 c.c. can be extended by crying to 160 c.c. In instances of depression of respiration brought about by premedication, anæsthetic drugs, muscle relaxants, or in intrathoracic operations, the tidal air and minute volume can be controlled by manual compression on the breathing bag or intermittent closure of the open arm of the Ayres T-tube. As a result, adequate oxygenation can be maintained.

It is often argued that with assisted or controlled inspiration the return flow of blood to

the heart loses the advantage provided by a decreased intrathoracic pressure. However, an adequate ventilation of the lungs far outweighs this disadvantage. For some years, we did allow the patients to breathe on their own through the endotracheal tube and anæsthetic apparatus. But we have found that manual compression on the breathing bag alleviates obstruction of respiration caused by soda lime, inhalation tubing and valves, and endotracheal tube.

All anæsthesia for major pædiatric surgery is carried on similarly to that in the adult, that is, a controlled oxygen supply; an assured free airway through an endotracheal tube; and a managed tidal air and minute volume. Further, all anæsthetic agents employed in adults can be utilized in the infant and young child.

Criticism is often levelled at the frequent use of endotracheal tubes in infants because of the extremely small airway. However, after several years of using endotracheal tubes in infants, we have had only 3 cases of tracheotomy, and 2 of these occurred many years ago. With the present practice of sterilized endotracheal tubes, minimal analgesic lubrication, gentle intubation, a cool moist atmosphere in instances of laryngeal obstruction post-operatively, then tracheotomy will be even less frequently required. Furthermore, a granuloma of the vocal cords in infants or children is practically unheard of, whereas it is not uncommon in adults. But, the most cogent argument in favour of endotracheal intubation is that the full control of the airway which it provides has saved many lives. On the other hand, the possibility of post-operative traumatic laryngitis is a small price to pay for safety.

During the past few years, it has been felt that under certain circumstances reduction in the oxygen demand may be beneficial. The method employed is very simple—it is the anæsthetization of the infant or child with cyclopropane; intubation with or without succinylcholine; controlled breathing; and then insertion of the intravenous needle into the vein while the veins are still dilated. This is followed by the placing of the patient in a tub the floor of which is coated with crushed ice covered with a sheet. A sheet is then placed over the patient and crushed ice scattered over it. In about 30 to 45 minutes the heart rate will be slowed considerably. When the heart rate is about 100, removal of the patient from the ice on to the operating-room table is followed by a further slowing of the heart-rate and a drop in temperature. We prefer to keep the heart-rate not lower than 50 per minute in the case of older children, and about 70 in infants. With such a heart-rate, the patient's temperature will read from 28° to 30° C.

Two of our emergency Pott's operative cases, under 1 year of age, died on the operating-room table. Several hypoxic signs occurred when the left pulmonary artery was clamped, indicating an inadequate right pulmonary circulation.

One coarctation case went into ventricular fibrillation immediately after the surgical clamps were removed from the aorta. The cause of the fibrillation was probably a severe drop in blood pressure following the clamp removal. Employment of an electrical defibrillator and cardiac massage over a 37-minute period finally resulted in a rhythmical contraction of the heart. Recovery of the patient was uneventful.

In conclusion, the adaptation of modern methods and benefits of adult anæsthesia should ultimately bring about a marked reduction in the anæsthetic death-rate in the infant and young child.

Table I gives a summary of the results in 149 cases.

TABLE I.

| | Number | Deaths |
|---|---|---|
| I. CARDIAC | | |
| A. Cyanotic Heart Disease | | |
| Tetralogy of Fallot .. .. | 21 | 2 |
| Pulmonary stenosis .. .. | 7 | — |
| Pott's for revision .. .. .. | 9 | 4 |
| Blalock for revision .. .. | 2 | 1 |
| Undiagnosed .. .. .. | 1 | 1 |
| Tricuspid atresia .. .. .. | 2 | 1 |
| Absence pulmonary artery .. .. | 1 | 1 |
| Cardiac cath. pul. atresia .. .. | 3 | 1 |
| Pulmonary valvotomy .. .. | 2 | — |
| Angiogram .. .. .. .. | 3 | 1 |
| | 51 | 12 |
| B. Acyanotic Heart Disease .. .. | 73 | 1 |
| II. NON-CARDIAC (including laparotomies and craniotomies) .. .. | 25 | 3 |
| Total | 149 cases | 16 deaths |

## BOOKS RECEIVED FOR REVIEW

**Adams (J. C.).** Outline of orthopædics. pp. viii + 423. Edinburgh and London: Livingstone. 32s. 6d. 1956.

**Ambrose (G.), and Newbold (G.).** A handbook of medical hypnosis. pp. xiv + 255. London: Baillière, Tindall and Cox. 21s. 0d. 1956.

**Asami (Y.), and Higasi (K.), eds.** Borderland problems between physical chemistry and physiology. (Monograph Series of the Research Institute of Applied Electricity, No. 5.) pp. 130. Sapporo, Japan: Research Institute of Applied Electricity, Hokkaido University. 1955.

**Bolton (E.), and Goodwin (D.).** An introduction to pool exercises. pp. 48. Edinburgh and London: Livingstone. 5s. 0d. 1956.

**Carpenter (P. L.).** Immunology and serology. pp. viii+351. Philadelphia and London: Saunders. 45s. 6d. 1956.

**Conn (H. F.), ed.** Current therapy 1956. pp.xxx+632. Philadelphia and London: Saunders. 77s. 0d. 1956.

**German Medical Journal.** Monthly English language edition of *Deutsche Medizinische Wochenschrift*. Vol. **1**, No. 1, pp. 1-36. Stuttgart: Georg Thieme. Annual subscription 30s. 0d. January 1956.

**Medicamundi:** a quarterly journal for the medical world. Vol. **1**, Nos. 1, 2 and 3, pp. 1-88. Eindhoven, Holland: Philips. (London: Cleaver-Hume.) Annual subscription 21s. 0d. ($3.00). 1955.

**Mitchell (G. A. G.).** Cardiovascular innervation. pp. xii + 356. Edinburgh and London: Livingstone. 55s. 0d. 1956.

**Moriyama (H.).** Immunity. pp. x + 203. Tokyo: Shonan Hygiene Institute, Kamakura. $5.00. 1955.

**Moriyama (H.).** The nature of viruses and the origin of life. pp. xii + 454. Tokyo: Shonan Hygiene Institute, Kamakura. $7.00. 1955.

**Paterson (D.), and Newns (G. H.).** Modern methods of feeding in infancy and childhood. 10th edit. pp. 188. London: Constable. 15s. 0d. 1955.

**Roxburgh (A. C.).** Common skin diseases. 10th edit. pp. xxxii + 516. London: Lewis. 30s. 0d. 1955.

**Sodeman (W. A.).** Pathologic physiology: mechanisms of disease. 2nd edit. pp. xxx +963. Philadelphia and London: Saunders. 91s. 0d. 1956.

**Spector (W. S.), ed.** Handbook of toxicology. Vol. **1**. Acute toxicities of solids, liquids and gases to laboratory animals. pp. viii+408. Philadelphia and London: Saunders. 49s. 0d. 1956.

**Studies on Fertility.** Including papers read at the Conference of the Society for the Study of Fertility, Birmingham, 1955. Being Vol. VII of the Proceedings of the Society. Edited by R. G. Harrison. pp. x+156. Oxford: Blackwell. 25s. 0d. 1955.

*Proceedings of the Royal Society of Medicine* Vol. 49 161

# Section of General Practice

President—GEOFFREY BARBER, O.B.E., M.A., M.B.

[*November 16, 1955*]

## SYMPOSIUM ON THE TREATMENT OF CEREBROVASCULAR DISEASE

**Dr. R. Crosbie Walsh:**

*Stellate Ganglion Block in the Treatment of Cerebrovascular Disease*

Anæsthesia or blocking of the stellate ganglion is of comparatively recent origin, and was first described by Leriche and Fontaine (1934). I started performing this injection in general practice some four years ago, largely as a result of the gross inadequacies in the routine treatment of hemiplegia following cerebrovascular catastrophes. Patients who have sustained such a lesion frequently either linger in bed or at the most in a chair for many months, and often for years before they have another catastrophe. Treatment is usually essentially nihilistic. Often the best that can be done is to send the patient by ambulance to the physiotherapy department of the nearest hospital where a certain amount of passive movement of the joints, or at most a few active contractions of isolated muscles, is obtained after many months' effort, this only to be vitiated by a further stroke or after confinement to bed with an intercurrent infection. I have tried during these four years to assess my results accurately.

The stellate ganglion is formed by the fusion of the inferior cervical and the first thoracic ganglia. It is about 2 cm. long and 1 cm. across. Often this fusion is incomplete, and when this occurs the two separate ganglia exist in close proximity to each other. This actually occurs in 18% of cases (Jamieson *et al.*, 1952).

The stellate ganglion lies behind the first portion of the vertebral artery in the space between the transverse process of C.7 and the neck of the first rib. Here it is in close relationship to the posterior aspect of the subclavian artery at its fusion with the inferior thyroid and the first intercostal artery. On the left side, as the apex of the lung is an inch lower than on the right, it does not form such close relationship, but on the right side the higher apex is in very close proximity to the ganglion. This point is particularly important when discussing the various techniques of blocking the stellate ganglion. As the ganglion is surrounded by areolar tissue anæsthetic fluids which are injected near it diffuse rapidly over a very wide area (Bonica, 1953). The sympathetic innervation of the whole of the head and neck pass through the stellate ganglion as well as the fibres from the intermediate and middle cervical ganglia. Much of the sympathetic innervation of the upper extremity passes through the ganglion via the brachial plexus. In addition, the inferior cardiac nerve receives two or three roots from the medial side of the ganglion. Fig. 1 shows the gross anatomy diagrammatically as a transverse section of the neck of the level of C.7.

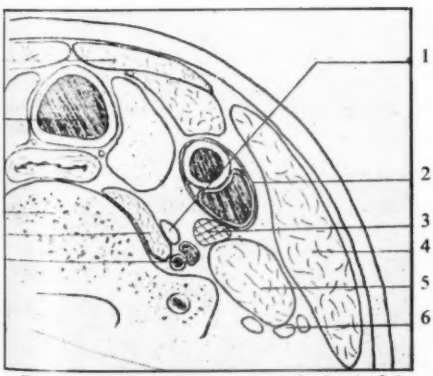


FIG. 1.—Section of the neck at the level of the lower border of the 7th cervical vertebra.
1. Stellate ganglion. 2. Carotid sheath. 3. Apex of pleura. 4. Sternomastoid. 5. Scalenus anticus. 5. Brachial plexus.

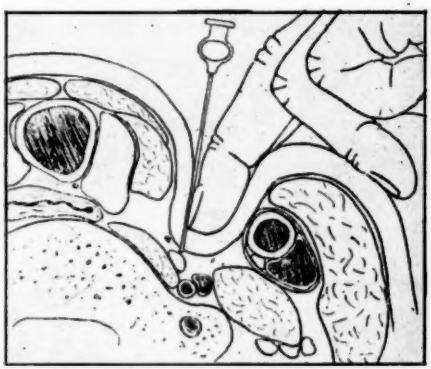

FIG. 2.—Section of the neck at the level of the lower border of the 7th cervical vertebra showing diagrammatically the fingers in situ with the needle inserted.

The stellate ganglion has an alarming array of vital structures in front of it. In their original description Leriche and Fontaine (1934) described an anterior approach. This method, however, I find difficult as bony landmarks are not clearly defined. A supero-external route was described by Arnulf (1938). An anterior type of approach, which is in fact an anterior lateral method was described by Ochsner and De Bakey (1939). A further antero-lateral approach was described by Volpitto and Risteen (1943), and a descending infiltration method which I find rather complicated was described by De Sousa Pereira (1945).

I have had difficulty with these methods, all of which are elaborate, and I use exclusively the simple anterior method which, as far as I can discover, was originally described by Findley and Patzer (1945). This last method is rapid and, I think, it produces the minimum of complications. I have treated as many as 20 patients in two hours using this method.

This technique is accomplished by lying the patient supine with a nurse holding the head, with both hands forming a cup under the occiput, so that she is actually taking the weight of the head and neck. This relaxes the sternomastoid muscles and allows them to be retracted laterally more easily with the fingers. The head must not be flexed but held in a neutral position. After preparing the neck with spirit the index and middle fingers separated by $\frac{1}{2}$ in. are pressed along the medial border of the sterno-mastoid muscle 1 in. above its sterno-clavicular insertion. Firm pressure is applied internally and laterally until the transverse process of C. 7. is felt. A 10 c.c. record syringe with a number 5 serum needle attached containing 10 ml. of 1% procaine solution is held in the right hand and the needle is inserted at a right angle along the nail of the index finger. The needle passes along the lateral border of the trachea and when it has been inserted an inch to an inch and a half the transverse process of the 7th cervical vertebra should be felt. The needle is then withdrawn very slightly and the aspiration test performed. This is essential particularly in view of the large number of small vessels around the ganglion. If this is negative the whole of the procaine is then injected.

Fig. 2 shows diagrammatically the fingers in situ with the needle inserted. The carotid sheath is pushed laterally and the apex of the lung depressed should it come up to this level.

Figs. 3 and 4 are X-rays taken after the injection of 10 c.c. of radiopaque material and within a very short period of time the dye is diffused over a wide area.

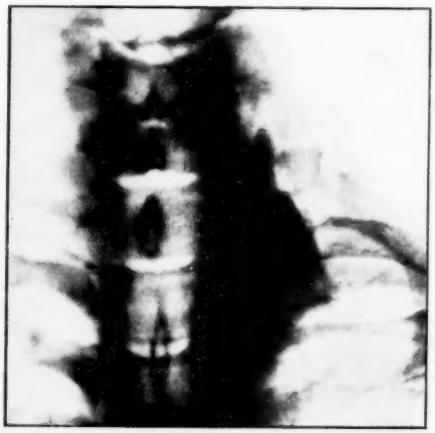

FIG. 3.—Antero posterior view of the neck immediately after the injection of 10 c.c. of dye.

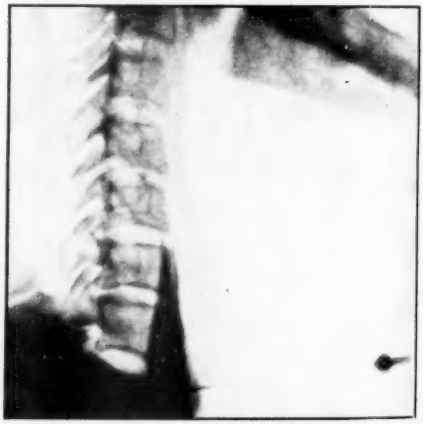

FIG. 4.—Lateral view of the neck immediately after the injection of 10 c.c. of dye.

The lateral view shows how far down the material diffuses. There appears to be no doubt that very much more than the stellate ganglion is in fact anæsthetized and with sufficient solution it should be possible to block the upper 5 or 6 dorsal ganglia with this technique.

Occasionally during this injection sharp pain is felt either down the arm or in the region of the heart. This is, I think, due to piercing the ganglion with the needle and when this occurs the procaine should be injected without delay to vitiate the effect of the physical stimulation of the ganglion.

The complications are directly related to the anatomy of the region and may be classified as vascular, pleural and neurological. The commonest vascular complication is putting the needle into the vertebral artery or vein. This, however, is easily recognized with the aspiration test, and when it occurs if the needle is withdrawn a few millimetres it should be well clear of the vessel. It is possible to transfix the common carotid artery, but with the method I have described this must be very rare. A pneumothorax can be produced, particularly when the right side is injected. Emphysematous bullæ are sometimes ruptured but this does not appear to be a serious complication. The neurological complications are in relation to the dura. It is possible to insert the needle into the subdural space. This has occurred once only in my series and was fortunately recognized quickly and no harm resulted.

I think undoubtedly the anæsthetic agent of choice is procaine. Procaine is relatively harmless if it is injected into a blood vessel or even the pleura. Xylocaine is more toxic and not without danger if injected into the pleura or into a blood vessel. I have no experience of using alcohol as this is liable to leave a painful neuritis (Bonica, 1953). I think that if permanent destruction of the ganglia is required it is better to do this surgically.

Successful blocking is shown by the rapid appearance of Horner's syndrome. I believe it is fundamental to the success of the manœuvre to obtain a Horner's syndrome otherwise the stellate ganglion has not, in fact, been anæsthetized. In fact all cases where this has not occurred have been excluded from the series. This, I think, accounts for many of the anomalies in the results published.

My largest series of cases is for upper motor neurone lesions which occur after a cerebral catastrophe, the commonest of which is, of course, a hemiplegia following a cerebral thrombosis. It is important to differentiate fully between cerebral thrombosis and cerebral hæmorrhage, as the block therapy should not be instituted when extravasation has occurred in the subdural space for at least five days (Butt and Mathers, 1948). Whereas Aring and Merritt (1935) believe this is possible in every case, I am sure mistakes must be made particularly where laboratory facilities are not available, and it has not been my practice to lumbar puncture as a routine. I think the most important test is to test for the presence of neck rigidity. When this is present it is very much more suggestive of hæmorrhage and not thrombosis (Walsh, 1954).

If improvement takes place after the first injection it is worth injecting bilaterally on alternate days, possibly for a total of three or four injections. If subsequently there is deterioration a further series of three injections can be given. If, on the other hand, there is no improvement after two injections it is useless to continue (Walsh, 1954). In hospital practice it is possible to use a wide bore needle and to pass a polythene tube through the needle leaving the tube in situ. By this means the nursing staff can inject the solution twice a day. I do not, however, consider this suitable for normal domiciliary practice.

Table I shows the results of treating a total of 198 cases. It can be seen from the figures

TABLE I.—RESULTS OF TREATMENT OF CEREBRAL CATASTROPHES WITH STELLATE GANGLION BLOCK.

| Time lapse | No. | Complete recovery | Good | Fair | No improvement |
|---|---|---|---|---|---|
| Within 24 hours | 41 | 23 | 9 | 0 | 9 |
| ,, 2–7 days | 52 | 15 | 13 | 10 | 14 |
| ,, 1– 4 weeks | 30 | 3 | 9 | 9 | 9 |
| ,, 1– 6 months | 38 | 0 | 0 | 11 | 27 |
| ,, 6–12 months | 37 | 0 | 0 | 9 | 28 |

that of 41 cases treated within twenty-four hours 23 made a complete recovery, and 9 showed excellent improvement. This compares at the other end of the scale with those cases which were not treated for six to twelve months, and it is interesting to note that of these 37, 9 showed some improvement.

More recently I have been using bilateral stellate block in the treatment of senile dementia and senile arteriosclerotic lesions (Walsh, 1955). It is difficult to assess the value but out, of the 14 cases treated 9 appeared to show considerable improvement. This improvement appeared to be maintained for a period of one to six weeks. 3 cases had subsequent injections and 2 cases had maintained improvement for periods of over six months. Karnosh and Gardner of Cleveland (1947) described the treatment of 3 cases of mental depression treated with stellate block. These 3 patients all improved.

I feel that the rationale of using it is that where there is a diminished blood flow this is improved by inhibiting the sympathetic and either by relieving the vasospasm or by increasing the flow through the anastomotic vessels, and I am quite certain that there is a place for this treatment in these conditions.

In conclusion, I should just like to add the other conditions for which I find it of use,

although these are not strictly cerebrovascular. Bilateral stellate block will usually relieve severe cardiac pain due to angina pectoris and will very often relieve the residual pain of an old coronary thrombosis, particularly where this is longstanding, although there is considerable controversy as to whether this is desirable. It is extremely useful for œdema of the chest and arm following radical mastectomy, and is specific in Raynaud's disease, although it should be reserved for the severe cases.

SUMMARY

Approximately 50% of patients with hemiplegia following cerebral thrombosis improve after stellate block. Where improvement occurs it is so dramatic and instantaneous that it cannot be attributed only to the natural course of the disease. It is not a panacea. It does offer a safe and simple procedure in the early treatment of one of the more common depressing conditions which one meets in a practice where there is more than the normal proportion of elderly patients.

Acknowledgments. I am grateful to Dr. Russell M. Davies (1952), and to the Editor of *Anæsthesia* for permission to use Figs. 1 and 2.

REFERENCES

ARING, C. D., and MERRITT, H. H. (1935) *Arch. intern. Med.*, **56**, 435.
ARNULF, G. (1938) *Pr. méd.*, **46**, 1726.
BONICA, J. J. (1953) The Management of Pain. London.
BUTT, T. C., and MATHERS, F. (1948) *J. Fla. med. Ass.*, **35**, 285.
DAVIES, RUSSELL M. (1952) *Anæsthesia*. **7**, 151.
DE SOUSA PEREIRA, A. (1945) *Arch. Surg., Lond.*, **50**, 152.
FINDLEY, T., and PATZER, R. (1945) *J. Amer. med. Ass.*, **128**, 1217.
JAMIESON, R. W., SMITH, D. B., and ANSON, B. J. (1952) *Quart. Bull. Northw. Univ. med. Sch.*, **26**, 219.
LERICHE, R., and FONTAINE, R. (1934) *Pr. méd.*, **42**, 849.
KARNOSH, L. J., and GARDNER, W. J. (1947) *Cleveland Clin. Quart.*, **14**, 133.
OCHSNER, A., and DE BAKEY, M. (1939) *Surgery*, **4**, 491.
VOLPITTO, P. P., and RISTEEN, W. A. (1943) *Anesthesiology*. **4**, 403.
WALSH, R. C. (1954) *Brit. med. J.*, ii, 684.
—— (1955) Old Age in the Modern World. London.

**Sir Russell Brain:**

*Anatomical and Physiological Factors in Treatment*

Recent advances in our knowledge of the cerebral circulation have shown how complex it is and how much about it is still unknown. The following Table shows the main factors as far as they are at present understood.

FACTORS IN THE CEREBRAL CIRCULATION

| | |
|---|---|
| Blood pressure | Hypertension<br>Hypotension |
| Resistance of cerebral vessels | Structural narrowing (atheroma, &c.)<br>Structural dilatation (atheroma, &c.)<br>Tonus (influence of $CO_2$ and $O_2$ and nervous system) |
| Collateral circulation | Circle of Willis<br>External carotid artery |
| Nutritional factors | Hæmoglobin<br>Vitamins |

*The blood pressure.*—The source of the cerebral circulation is obviously the head of blood pressure supplied to the internal carotid and vertebral arteries. When, from any cause, this falls sufficiently far, loss of consciousness occurs, and, if hypotension is prolonged, there may be permanent damage to the brain. Hypertension would produce an increased blood flow through the brain if the resistance of the cerebral vessels remained the same. However, in states of hypertension the tonus of the cerebral vessels is increased and may even be doubled. Therefore, as Kety (1955) points out, the cerebral blood flow remains normal, because the increased resistance parallels the increased blood pressure. This has important implications for the treatment of patients with hypertension who already show signs of cerebral damage. Kety observes that a fall of blood pressure does not cause immediate and complete relaxation of the cerebral vessels. Consequently the cerebral blood flow falls and some degree of cerebral anoxia may occur. It is not uncommon for hypertensive patients who have never had any cerebral symptoms to exhibit mild ones if their blood pressure is lowered too rapidly by means of hypotensive drugs. If a hypertensive patient already has sufficient atheroma in the cerebral arteries to cause structural narrowing he may not be able to maintain his circulation through such vessels without the aid of his hypertension. In such a case lowering of the blood pressure may cause permanent damage.

*Resistance of the vessels.*—The second main feature in the control of the cerebral circulation

is the resistance of the vessels. Here we still have much to learn. The importance of narrowing due to atheroma is obvious. But atheroma may also produce dilatation. By tonus I mean that degree of sustained contraction of a vessel which occurs independently of structural change, though it is possible, indeed probable, that structural change may be one of its causes. I have already mentioned the state of increased tonus which occurs in patients with hypertension. An extreme degree of this appears to be the cause of hypertensive encephalopathy as Byrom (1954) has recently shown in his experimental investigations. It is in the treatment of hypertensive encephalopathy occurring in a patient without serious structural change in the cerebral vessels that hypotensive drugs are particularly valuable. The term "spasm" may be applied to a brief attack of increased tonus of a cerebral artery. Our clinical predecessors were apt to attribute transitory disturbances of the cerebral circulation in patients with degenerative cerebral vascular disease to attacks of spasm. Subsequently this view became rather discredited, supposedly on physiological grounds, but cerebral arteriography has taught us how readily the internal carotid artery may go into spasm, and there is some reason to think that this may also happen in its branches. If so, local vascular spasm may be a factor in interfering with the cerebral circulation, and possibly, even, precipitating cerebral thrombosis, but this is still largely speculative.

Recent pharmacological investigations have shown how little the cerebral circulation is influenced by the ordinary vasoconstrictor and vasodilator drugs. Kety in his recent review states that the administration of carbon dioxide in a concentration of 5% to 7% increases the cerebral blood flow to 75% above normal. Anoxia has a similar effect, while breathing a high concentration of oxygen leads to vasoconstriction.

Though cerebral vascular spasm may be induced reflexly, the central nervous system seems to have little local influence upon the cerebral circulation, at least in man. Schmidt (1950), recently reviewing this subject, states that although constriction of cerebral blood vessels has been demonstrated as the result of stimulation of sympathetic nerves, the significance of this finding is by no means clear, and in his view the signs of cerebral vasoconstriction revealed by direct instrumentation of the cerebral cortex in the cat or rabbit should be regarded as a vestigial remnant of an undesirable type of control rather than as an expression of a physiological useful and important mechanism. The available evidence, however, indicates that the extracranial parts of the cephalic circulation are much more influenced than the intracranial by impulses carried by the cervical sympathetic nerves.

The assessment of the value of sympathetic block in the treatment of cerebral vascular lesions is by no means easy. I think it would be rash in the present state of our knowledge to say on theoretical grounds it could be of no value. Experimental observations on animals may not be directly applicable to the much more complex conditions which occur in pathological states in man. Moreover, as we shall see shortly, there is evidence for the existence of a collateral supply to the cerebral circulation through the external carotid, though this is probably normally insignificant. However, in an emergency, dilatation of this route might be important. We need statistically controlled studies, for spontaneous rapid and virtually complete recovery from what appeared to be a very serious cerebral vascular lesion is a common experience in the absence of any form of treatment.

*The collateral circulation.*—The circle of Willis is a favourite subject for the demonstration of a collateral circulation, but it is only recently, since we have learned to diagnose thrombosis

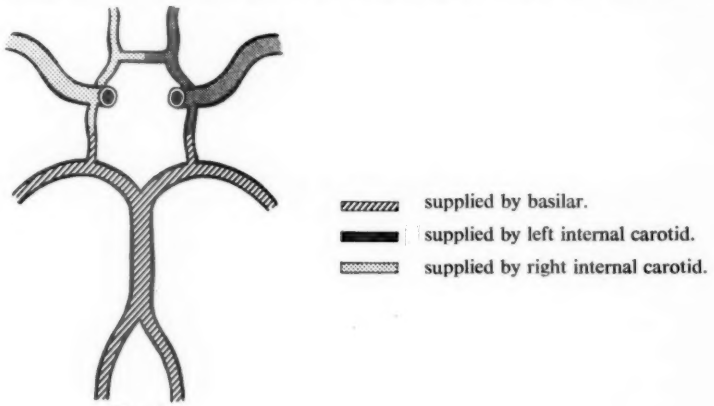


FIG. 1.

of the internal carotid artery, that we have appreciated its true value in that role. Fig. 1 shows the normal distribution of the blood to the brain derived from the basilar artery and the two internal carotid arteries respectively as shown by the experimental work of McDonald and Potter (1951) and applied to man by Symonds (1955). There is evidence that when one internal carotid artery is blocked the blood supply to the brain is shared between the basilar artery and the remaining internal carotid artery. Whether ischæmic cerebral symptoms occur depends mainly, as Symonds has pointed out, upon how slowly the obstruction of the internal carotid occurs, upon the patency of the collateral circulation, especially the anterior communicating artery and upon the blood pressure available to establish the collateral circulation. Vasodilator drugs do good only if they dilate the cerebral vessels more than they lower the blood pressure. That is why I think it is important that a patient suffering from a cerebral ischæmic episode should be got out of bed as soon as his condition permits. I can find no justification for the traditional practice of keeping these patients in bed for weeks. If they are allowed to move about as much as possible their cerebral circulation is less likely to fall off and they are less likely to have thromboses elsewhere.

It should be noted that the usual site for thrombosis of the internal carotid artery is about 1 cm. above the bifurcation. Of course if thrombosis should occur in, or extend into, the point at which the internal carotid is linked with the circle of Willis, the collateral circulation could not occur. Here let me stress a point which is important for the interpretation of symptoms. What is the precise cause of those transitory disturbances of cerebral function which so frequently occur in patients suffering from atheroma of the cerebral vessels, particularly of the internal carotid, and especially in the earlier stages? Various interpretations have been put forward, but I believe Symonds is right when he said that "this episodic loss of function, which must be ischæmic, is not due to any fresh vascular obstruction, but to a temporary failure of the compensatory mechanisms". In any case I would stress the distinction between cerebral ischæmia and cerebral thrombosis. Thrombosis may be inferred from arteriography, or verified at autopsy but clinically it is usually impossible to say more than that a patient has an ischæmic lesion. We cannot be sure that thrombosis has occurred, indeed a severe hemiplegia may be encountered in a patient whose internal carotid artery, though atheromatous, is still patent.

*Nutritional factors.*—I mention these because we ought not to allow our interest in the grosser aspects of the cerebral circulation to cause us to overlook the fact that any form of interference with the blood supply to the brain reduces also the supply of those substances necessary for its nutrition and normal function. If a patient is anæmic the brain will work better if his hæmoglobin is raised to normal. It is certainly rational to give vitamins, especially those of the B group, in the hope that by raising their level in the blood they will be more available to the nervous system. This should make it easier for the brain to utilize glucose.

In conclusion let me stress once again the complexity of the cerebral circulation and our ignorance of many of the factors involved. If often we cannot do as much good as we should like, we can at least be careful that our treatment does no harm, and that in our endeavour to gain on the blood pressure swings we do not lose on the cerebral roundabout.

## REFERENCES


Byrom, F. B. (1954) *Lancet*, ii, 201.

Kety, S. S. (1955) In: Neurochemistry. Editors: K. A. C. Elliott, I. H. Page, and J. H. Quastel. Springfield and Oxford; p. 294.

McDonald, D. A., and Potter, J. M. (1951) *J. Physiol.*, **114**, 356.

Schmidt, C. F. (1950) The Cerebral Circulation in Health and Disease. Springfield.

Symonds, C. (1955) *Brit. med. J.*, i, 119.


**Mr. M. A. Falconer,** *in absentia,* read by **Mr. J. G. Hamilton:**

### *Progress in the Surgical Treatment of Spontaneous Cerebral Hæmorrhage*

Spontaneous cerebral hæmorrhage includes two main groups of conditions, intracerebral hæmorrhage and subarachnoid hæmorrhage. The clinical distinction between the two is often difficult and arbitrary, for both are usually characterized by a sudden and unheralded onset of severe headache followed quickly by dazedness or loss of consciousness, while in both blood is usually present in the cerebrospinal fluid on lumbar puncture. Primary intracerebral hæmorrhage is of course much the more common and chiefly occurs in patients aged over 50 years who suffer from advanced arterial degeneration. In such persons it is usually quickly fatal and is outside the scope and possibilities of surgery. But a small minority of cases, containing patients of all age groups, survive the first two or three days, and in them the bleeding may come from an aneurysm, malformation, or even some undetected cause. Such cases present a challenge to surgery and many of them can be benefited (Falconer, 1952; Beck, 1953).

Spontaneous subarachnoid hæmorrhage is less common. Typically there are no localizing neurological signs, and most persons survive the initial symptoms. As, however, bleeding also often occurs into the cerebral substance, and sometimes even into the subdural space, while the causal lesion itself may produce focal disturbances, neurological signs such as a III cranial nerve palsy, a hemiparesis, a hemianopia, or a frontal lobe syndrome are quite common. Primary subarachnoid hæmorrhage, once erroneously thought to occur chiefly in young adults, can appear at any age period, and indeed reaches its peak incidence in the 40 to 60 years age group (Falconer, 1954; Walton, 1955). It probably occurs in approximately one person each year in every 10,000 of population (Falconer, 1950).

Subarachnoid hæmorrhage, although not as deadly as primary intracerebral hæmorrhage, is still a very serious condition. Statistics from many general hospitals where reliable records are kept, and where in the past patients have been treated by prolonged bed rest show mortality rates ranging from 45 to 60% (Falconer, 1951; Walton, 1955). An important factor relating to this is the frequency of recurrent bleeding. Indeed recurrence of hæmorrhage occurs in more than half of those patients who survive the initial attack and reaches its peak incidence between the second and fourth weeks (Falconer, 1951; Mount, 1951; Walton, 1955). Even the later prospects of patients who survive six weeks or so and then leave hospital are forbidding, for both Hyland (1950) and Walton (1955) have shown that if they are followed up for a number of years a fifth will be found to have died of delayed recurrent bleeding. Half of these deaths occur in the first six months. Ask-Upmark and Ingvar (1950) put the prognosis of subarachnoid hæmorrhage succinctly when they stated that out of 5 patients treated conservatively, 3 will die sooner or later from its effects, 1 will be left crippled, and only 1 will make a good recovery.

Fortunately by timely surgical intervention it is possible greatly to improve the prospects of patients. Clinico-pathological studies indicate that in about 80% of cases the responsible lesion is a bleeding saccular aneurysm, in 10% an arteriovenous malformation (angioma), and in the remaining 10% an assortment of lesions (Walton, 1955). Most of these lesions are amenable to surgery, and can be demonstrated during life by bilateral carotid arteriography. Thus in 1954 I reported 148 consecutive patients with subarachnoid hæmorrhage investigated by arteriography, aneurysms being demonstrated in 67% of them (Table I).

TABLE I.—SPONTANEOUS SUBARACHNOID HÆMORRHAGE

| | 148 patients | | |
|---|---|---|---|
| | Patients | % of group | Operative mortality |
| Aneurysms .. .. .. .. | 100 | 67% | 13% |
| Arteriovenous malformation .. .. | 12 | 8% | 0 |
| Unexplained intracerebral hæmatomas | 7 | 5% | 0 |
| Cerebral tumours .. .. .. | 3 | 2% | 33% |
| No lesion demonstrated .. .. | 26* | 18% | Untreated (2 died in hospital) |

*Follow-up studies have since revealed 4 aneurysms.

Total hospital mortality for 148 patients=11%.

Other neurosurgeons, notably Mount (1951), Norlén (1952), Hamby (1952), and Small and his associates (1953) have all reported comparable results. With increasing experience once can better one's results. Thus my first 50 aneurysm patients, reported in 1951, were operated on by various procedures with 9 deaths (18%) and 33 good recoveries. These figures were, I felt, a distinct improvement on the prospects of these patients for most of them were gravely ill (half of them with recurrent hæmorrhages) and consequently had a worse prognosis had they been treated conservatively than the usual run of hospital cases (Falconer, 1951, 1952). But with increasing experience in the selection of patients and in the timing and technique of operation, my last 50 patients with aneurysms all operated on between January 1952 and July 1955 have had only 3 operative deaths (including 1 patient who died in hospital nine months after operation) and 38 satisfactory recoveries (Tables II and III).

TABLE II.—RESULTS OF OPERATIONS ON TWO SERIES OF 50 CONSECUTIVE PATIENTS WITH ANEURYSMS

| Series Year reported | Number of patients | Good results | Poor results | Deaths |
|---|---|---|---|---|
| 1951 | 50 | 33 (66%) | 7 | 9 |
| 1955 | 50 | 38 (76%) | 9 | 3 |

TABLE III.—OPERATIONS ON 50 CONSECUTIVE ANEURYSM PATIENTS
(up till July 1955)

| Site and treatment | Operation results: Good | Poor | Died | Late deaths | Total |
|---|---|---|---|---|---|
| INTERNAL CAROTID | | | | | |
| Direct attack .. .. | 6 | 1 | 0 | 0 | |
| Carotid ligation .. .. | 6 | 2 | 0 | 1 | 16 |
| CAROTID BIFURCATION | | | | | |
| Direct attack .. .. | 1 | 0 | 0 | 0 | |
| Carotid ligation .. .. | 1 | 0 | 1 | 0 | 3 |
| ANT. COMMUNICATING | | | | | |
| Direct attack .. .. | 10 | 0 | 1 | 1 | 12 |
| ANT. CEREBRAL | | | | | |
| Direct attack .. .. | 1 | 0 | 1 | 0 | 2 |
| MIDDLE CEREBRAL | | | | | |
| Direct attack .. .. | 7 | 0 | 0 | 0 | 7 |
| BASILAR | | | | | |
| Vertebral ligation .. .. | 2 | 0 | 0 | 1 | 3 |
| MULTIPLE | | | | | |
| Direct attack .. .. | 1 | 2 | 0 | 0 | |
| Carotid ligation .. .. | 3 | 0 | 0 | 1 | 7 |
| | 38 | 5 | 3 | 4* | 50 |

*One patient died of coronary thrombosis, the remainder presumably of recurrent bleening.

There are several factors which make for success, and the first is the timing of arteriography and operation. The latter is the more crucial, for arteriography should be deferred until the stage is set for surgery. In general the optimum time for both arteriography and operation would appear to be towards the end of the first week following the initial hæmorrhage. Experience has shown that it is usually impossible by operation to revive a deeply unconscious patient, except in the occasional case where there is a massive intracerebral clot. It has been found that arteriography performed within two or three days of the onset of bleeding is apt to aggravate symptoms or even be followed by a transient hemiplegia, presumably due to vasospasm (Falconer, 1954), while such complications are usually avoided if arteriography is deferred till a little later. Thus it is impossible to save a small minority of patients. However, by operating towards the end of the first week it is still possible to save some of those who would otherwise have died of their initial attack, while at the same time preventing death from recurrent hæmorrhage before the peak incidence of recurrence develops.

The essential pre-operative investigation is bilateral carotid arteriography, and until this has been performed the site and cause of the hæmorrhage cannot be known (Figs. 1 and 2).

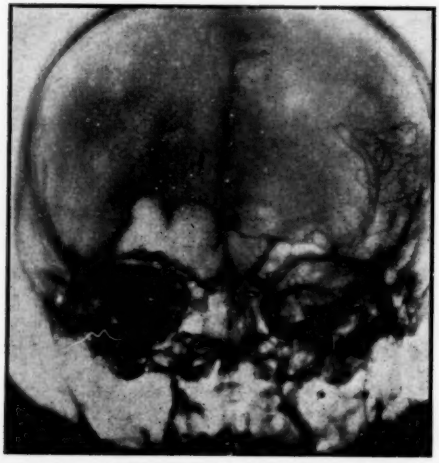

FIG. 1.—Arteriogram showing aneurysm (arrow) of anterior communicating artery, a site usually suitable for a direct operation.

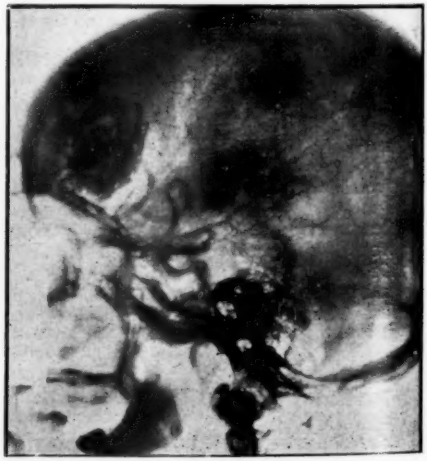

FIG. 2.—Arteriogram showing arteriovenous malformation at frontal pole, a site suitable for excision.

The technique employed is the usual percutaneous one, performed under local analgesia using 35% compound diodone solutions. This investigation will reveal most cerebral aneurysms and arteriovenous malformations as well as indicate the presence of moderate or large intracranial clots. Even in elderly or middle-aged persons with high blood pressure we perform percutaneous arteriography if the cardiovascular system seems otherwise healthy, for in many such patients a bleeding intracranial aneurysm is responsible for symptoms, and sometimes when the acute episode subsides, the blood pressure returns to normal. It is necessary to perform carotid arteriography bilaterally because my radiologist Dr. R. Hoare, and I have found two or more aneurysms present in 13% of our more recent aneurysm patients. It often requires considerable experience both in the technique of arteriography and in the interpretation of findings, to be certain whether or not an aneurysm is present, for the vast majority of bleeding aneurysms are small, ranging from 1·5 cm. diameter down to only 2 or 3 mm. (Falconer, 1954). Bilateral carotid arterigraphy is also useful for demonstrating the state of the collateral circulation through the circle of Willis, should carotid ligation prove necessary in treatment (Falconer, 1951). If carotid arteriography is negative we usually proceed a few days later to vertebral arteriography, for in from 5 to 10% of cases the aneurysms are situated on the basilar arterial tree.

The choice of the actual operative procedure depends on the site and nature of the lesion. Time does not permit me to consider this, except in the briefest fashion. I have done this more fully elsewhere (Falconer, 1951). Aneurysms on the intracranial internal carotid artery below the circle of Willis, for instance, are probably best treated by common or internal carotid ligation. A short period of compression of the carotid artery should always be tried before the ligature is placed permanently. If, however, the collateral circulation is inadequate, or bilateral internal carotid aneurysms are present, a direct attack is preferable. A direct attack is also preferable for aneurysms of the middle cerebral and anterior cerebral arteries. It is not difficult to expose any part of the circle of Willis, particularly if the patient's blood pressure is brought down routinely to 70 mm.Hg for a short time by hypotensive drugs such as Arfonad. Hypothermia as an additional aid in diminishing the circulation has so far not proved necessary. Once the aneurysm is exposed a whole variety of measures can be applied to it. If its neck is narrow this can be clipped or ligated. If the aneurysm is small it can be wrapped around with muscle. If large, proximal clipping of the feeding artery is sometimes feasible. Several times, particularly in the days before hypotensive measures were available, an aneurysm has burst when exposed, but I have generally managed to control the bleeding with muscle packs. Any intracerebral clot associated with an aneurysm should be sucked out. Aneurysms of the basilar artery can be treated by vertebral artery ligation, and on the posterior cerebral artery sometimes by clipping the neck of the aneurysm. Many arteriovenous malformations can be excised, but if they are inaccessible they can often be treated by proximal ligation of the feeding vessels (Falconer, 1954).

Surgery thus has a prominent part to play in the treatment of spontaneous cerebral hæmorrhage, and should be considered in all cases which survive the first few days, especially in the younger age groups. The lowering of mortality rates to low figures in the last three years has been due not only to improvement in operative technique, but also to the increasing tendency of colleagues to refer for operation their less gravely ill patients. There is no doubt that by timely surgery considerable help can be given to individual patients, and their prospects greatly improved. Even some of the patients with two or more aneurysms can be benefited (*see* Table III). The provision of neurosurgical facilities for the investigation, treatment, and after-care of these patients, however, still lags behind the needs.

I am grateful to Mr. J. G. Hamilton for compiling the Tables.

## REFERENCES


Ask-Upmark, E., and Ingvar, D. (1950) *Acta med. scand.*, **138**, 15.

Beck, D. J. K. (1953) *Arch. Middx. Hosp.*, **3**, 150.

Falconer, M. A. (1950) *Brit. med. J.*, i, 809.

—— (1951) *J. Neurol. Psychiat.*, **14**, 153.

—— (1952) *Lancet*, ii, 945.

—— (1954) *Proc. R. Soc. Med.*, **47**, 693.

Hamby, W. B. (1952) Intracranial Aneurysms. Springfield.

Hyland, H. H. (1950) *Arch. Neurol. Psychiat., Chicago*, **63**, 61.

Mount, L. A. (1951) *J. Amer. med. Ass.*, **146**, 693.

Norlén, G. (1952) *Proc. R. Soc. Med.*, **45**, 291.

Small, J. M., Holmes, J. MacD., and Connolly, R. C. (1953) *Brit. med. J.*, ii, 1072

Walton, J. N. (1955) *Canad. med. Ass. J.*, **72**, 165, 136.

**Dr. John H. Hunt:**

*The Treatment of Acute Emergencies in Cerebrovascular Disease*

During five years in general practice immediately after World War II, I saw 35 cases of cerebral thrombosis, 3 cases of cerebral embolus and 2 of proved hæmorrhage (although more of them probably had small bleedings). Only 7 of these 40 patients were unconscious when I was called in; all the rest were wide awake and only too aware of the blow that had befallen them.

The sudden onset of weakness of one hand without any other symptom, occurring in a housewife cooking the family dinner, a farmer driving his tractor, or a secretary in the middle of a busy afternoon's appointments or typing, will almost always be troublesome enough for the family doctor to be phoned. Even without weakness or numbness, a housewife with sudden temporary apraxia, for instance—the loss of purposeful movements—is as much disabled and as much disturbed as a cricketer with sudden hemianopia, or a politician with sudden aphasia. I well remember a dear old lady standing pathetically with a matchbox in one hand and a teapot in the other, saying, "I've made pots of tea all my life and now suddenly, for some reason or other, I just can't do it"—a sad example of apraxia, of cerebrovascular origin, occurring as a real emergency in general practice. The presenting symptom may sometimes be sudden incapacitating dizziness or headache such as occurs in subarachnoid hæmorrhage; one may recall the graphic newspaper descriptions of President Roosevelt's headache at the onset of his last illness.

The management by the family doctor of the milder degree of cerebrovascular emergency, which is not severe enough directly to threaten life but is incapacitating enough to be of the utmost importance to the patient and her friends, is by no means always straightforward or easy. What exactly is one to do if a person sitting next to one, say at a lunch party or in a cinema suddenly says he has tingling down the left side of his face, and that his left arm has gone numb and weak? Should the patient lie down or sit up? One would gather from some of the textbooks that he should hardly walk a step; but nine times out of ten he has got to do so; and there is little evidence that standing up and walking slowly really changes much the blood supply to the brain. One cannot very well carry a stretcher into a lunch party, and it is almost impossible to do so into the middle of a row of seats at a cinema. A farmer at work on his tractor will have to get back, with help, across the field to his farmhouse. Rather than wait for an ambulance, I have often found it better to take most of these patients straight home, or to hospital, in my car. They are then warm in bed with proper nursing in the shortest possible time, perhaps within half an hour.

Should the patient be given coffee, or brandy, or any other medicines? The drugs recommended in the textbooks for this stage are legion. It was at one time thought that some of the answers to these questions depended on whether the damage was due to thrombosis or hæmorrhage; the first needing stimulants and moving about, the second complete rest and even venesection. Nowadays it is generally agreed that the treatment of the two should be roughly the same; which is fortunate, because it is well-nigh impossible, often, to tell in the first few minutes what the lesion is. Whether it be thrombosis, hæmorrhage or embolus, the essential factor is to ensure an adequate blood supply to that part of the brain which is not irretrievably damaged. The patient should be made comfortable, reclining, with his head a little raised; his collar should be undone—that is most important. A drink of hot tea is better, I think, than brandy; and a hot bottle at the feet is of more comfort and better treatment of shock, and much easier to obtain, than is an ice-bag to the head. A mouthful or so of brandy may perhaps relieve the patient's anxiety; to send for it may give an onlooker who has lost his head something to do. Alcohol should not be given in large enough amounts to cause general vasodilatation, and vasodilator drugs are best avoided. They dilate blood vessels all over the body and those in the brain which need blood most may, as a result, receive less. No vasodilators we doctors can give can compare with Nature's local vasodilatation resulting from nearby cerebral ischæmia, and no cardiac stimulants that we prescribe will increase the cerebral circulation to the extent that Nature does by her reflex rise of blood pressure in these cases. With an anxious patient, and everyone around him extremely worried, there is still thought to be something almost magical in the doctor giving an injection in an emergency. As most of us know so well, an injection of almost any sort may be helpful as a calming influence on the patient and the onlookers. A small dose of intramuscular phenobarbitone is probably as useful as any so-called "cardiac stimulant" at this stage.

The symptomatic treatment of headache, dizziness, &c., may be urgently called for. Some of these severe headaches may only be relieved by intravenous pethidine or omnopon, combined perhaps with intramuscular Largactil. Omnopon is not as dangerous in these cerebrovascular emergencies as was once thought. I have found heroin useful for this type of severe headache.

Instructions must be given to the relatives as to what they should do should there be a deterioration in the patient's condition soon after the doctor has left. Even after quite a small cerebrovascular accident, without unconsciousness, the family doctor may have to spend considerable time and give a great deal of thought as to how best he may help the patient and the family throughout that difficult day.

Now we come to those more severe emergencies which directly threaten life. The sudden onset of unconsciousness (which comes on faster with hæmorrhage than with thrombosis, and faster still with an embolus) is of itself dramatic enough, and the doctor is nearly always sent for in a hurry. The emergency may happen anywhere. Not long ago I was called in to see a patient, deeply unconscious from cerebral hæmorrhage, who was still at the driving wheel of her car in a London street. Twice this year I have had to go to a flat, because the milkman on one occasion and the charwoman on another had been unable to get an answer to the door bell. At such times the family doctor may be called before the police; it is unwise to break into a house or a flat without police co-operation; when a 'phone message comes like that, I usually 'phone the local police before starting out, so that we arrive at the scene of emergency together. On the first of these two occasions an old lady of over 80, who lived in a third-floor flat and was terrified of burglars, had double-locked and bolted her front door in such a way that a battering-ram would have been needed to break it down. In the end the porter of the block of flats squeezed himself into the food lift, climbed in through the third floor kitchen window to find the patient, as we had rather expected, deeply unconscious on her bedroom carpet. When I was dealing with her, a message came through to say that the porter had himself been taken ill outside in the passage, and in a short time he was dead of a coronary thrombosis. That kind of situation is not in the textbooks and it needs a little sorting out by the family doctor.

Then there are the problems of transport which crop up with many of these unconscious patients. Sometimes the patient *must* be moved, as with the girl unconscious at the driving wheel of her car. One may sometimes be puzzled, however, as to whether a patient in bed at home should be moved or not. How many of these patients are really too ill to move? The answer is, I believe, "very few". If better treatment can be had elsewhere, and transport can be done carefully and well, a move is nearly always wise. During the war, when I was in the R.A.F. treating many head injuries in a large hospital serving Bomber Command in East Anglia, there was no neuro-surgeon to this hospital and we often had to move these extremely ill patients to the Head Injury Hospital, Oxford, a hundred miles or so distant. I often accompanied them on their journey, either by air or by road, some of them unconscious on the way, and I do not remember one deteriorating because of the journey.

A deeply unconscious patient may often be looked after at home by his family doctor quite satisfactorily, provided there is adequate nursing help; but treatment is usually best carried out in a general-practitioner hospital bed or in a nursing home. There are only about 6,500 general-practitioner beds in this country for 23,000 practising family doctors. We want more.

It is of the utmost importance that the doctor in charge should visit the patient frequently in the early stages, perhaps several times a day. Aspiration of mucus from the throat must be carried out frequently, perhaps every quarter of an hour in some cases, and the nurse may need careful instruction in this. I have found an electric sucker (which may be hired from one of the pharmaceutical firms) useful. The importance of keeping a good airway, and the difficulty in keeping the tongue from falling back in unconscious patients, are so well recognized in head injury hospitals, that some patients who are deeply unconscious have a tracheotomy done which, I am told, improves the prognosis considerably.

The unconscious patient is best nursed with his head on one or two pillows, and over to one side, the paralysed side being kept upwards because it is liable to crumple if underneath. Paralytic conjugate deviation of the head and eyes is away from the paralysed side, which helps the turning of the head in this position. The bowels can usually be left alone for a few days and then an enema is better than a purge. Special care must be taken to prevent any blockage of venous return of blood from the head, the development of pneumonia, distension of the bladder and urinary infection, bed sores and burns from hot bottles. I nearly always use penicillin prophylactically to prevent the development of pneumonia, and streptomycin to prevent urinary infection, which is especially important when patients have to be catheterized. No single antibiotic seems to be as good in these patients as a combination of penicillin and streptomycin, which may conveniently be given in a combined preparation

known as Crystamycin. Convulsions may need intravenous anti-convulsants; oxygen may be required for cyanosis, venesection if the blood pressure is unduly high, and atropine for pulmonary œdema. The shoulders and other joints should be put through a full range of movements once a day to prevent painful stiffness later. Lumbar puncture may relieve intracranial pressure better than anything else; it is seldom dangerous in these conditions if a fine needle is used, and the fluid drawn off slowly. Some patients recover consciousness quite soon after this manœuvre. What one is hoping for all the time in these unconscious patients, and what the relatives are praying for, is for some sign of improvement. A return of the corneal reflex and swallowing reflex, signs of returning consciousness and response to stimuli, are the points for which to watch.

The most important thing of all about the treatment of people who are unconscious is to ensure adequate hydration. Many unconscious patients die quickly simply because they do not receive enough fluids, especially if they have fever. If the swallowing reflex is not normal (and it seldom is in these cases) it is impossible to feed anything by mouth without the risk of something passing into a bronchus; and rectal feeding is unsatisfactory when there is incontinence. The passing of a thin nasal tube is nearly always the answer, and I myself believe that every patient in coma should have one. A thin nasal tube of rubber or polythene (rubber is softer than polythene but a little more difficult to manipulate) about one-third the diameter of an ordinary Ryle's tube, is usually easy to pass. To put fluid into the stomach, one can use a very much smaller, thinner and softer tube (size 3) than one does if one wants to suck fluid out (size 6 or 8) as after abdominal operations. With the help of such a nasal tube, a deeply unconscious patient may be kept alive for days and even weeks, with the doctor in control of fluid intake, nutrition, antibiotic and drug therapy all the time. It is as well to remember that even after long periods of unconsciousness, satisfactory recovery from cerebrovascular accidents may occur with minimal sequelæ, because some of the coma may be due to cerebral œdema, and it may be impossible to say at first how much final recovery will occur. It is always worth struggling on, especially with younger people, in the hope that one day the patient may turn the corner and make a degree of recovery that will surprise everyone. For this nasal feeding, one should give the patient three to four pints of fluid a day in small amounts at a time, containing at least 2,500 calories. An easy way to do this, and an easy one to remember, is to put down the tube every twenty-four hours, 4 pints of milk, 4 eggs, 4 ounces of sugar, the juice of 4 oranges and 4 saltspoonsful of salt, with what additional vitamins, antibiotics, sedatives, purgatives or other medicaments (such as digitalis if there is auricular fibrillation) that may be required. I have been impressed by the action of vitamin P in reducing the incidence of spontaneous subcutaneous ecchymoses in old people; recently, and purely empirically, I have been giving this vitamin to all my patients with strokes.

Lastly, the early stage of recovery has its own problems. When consciousness begins to return, as it may do after a few minutes or hours, the patient may become extremely restless—trying to pull out the nasal tube or to get out of bed. Extra sedatives may be necessary to carry the patient through this stage, and intramuscular Sodium Luminal or Sodium Amytal (0·2 gram) or paraldehyde (5 ml.) are useful. Bedsides may not necessarily be enough to keep a patient in bed; I had a patient the other day who climbed off the end of his bed and injured himself, in spite of bedsides and having a special nurse in the room. During the war we sometimes found it far better to allow a restless, semiconscious patient to sit up in an armchair, if he wished to do so, rather than to fight all the time to keep him in bed.